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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

HIV INTEGRASE INHIBITORS

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HIV INTEGRASE INHIBITORS

The present invention relates to novel compounds, their use as integrase inhibitors, processes for their preparation as well as pharmaceutical compositions and diagnostic kits comprising them. The present invention also concerns combinations of the present integrase inhibitors with anti-retroviral agents. It further relates to their use in assays as reference compounds or as reagents. The compounds of the present invention are useful for preventing or treating infection by HIV and for treating AIDS.

The virus causing the acquired immunodeficiency syndrome (AIDS) is known by different names, including T-lymphocyte virus III (HTLV-III) or lymphadenopathy-associated virus (LAV) or AIDS-related virus (ARV) or human immunodeficiency virus (HIV). Distinct families have been identified, such as HIV-1 and HIV-2. Hereinafter, HIV will be used to generically denote these viruses.

A common feature of retrovirus replication is the insertion by virally-encoded integrase of proviral DNA into the host cell genome, a required step in HIV replication in human T-lymphoid and monocytoid cells. The integration process takes place following reverse transcription of the viral RNA. First, the viral integrase binds to the viral DNA and removes two nucleotides from the 3' end of the viral long-terminal repeat (LTR) sequences on each strand. This step is called 3' end processing and occurs in the cytoplasm within a nucleoprotein complex termed the pre-integration complex (PIC). Second, in a process called strand transfer, the two strands of the cellular DNA into which the viral DNA will be inserted, i.e. the target DNA, are cleaved in a staggered fashion. The 3' ends of the viral DNA are ligated to the 5' ends of the cleaved target DNA. Finally, remaining gaps are repaired, probably by cellular enzymes.

It is known that some antiviral compounds which act as inhibitors of HIV replication are effective agents in the treatment of AIDS and similar diseases, including reverse transcriptase inhibitors such as azidothymidine (AZT), ddC, stavudine, didanosine, nevirapine, abacavir, lamivudine, delavirdine, tenofovir and efavirenz and protease inhibitors such as indinavir, saquinavir, amprenavir, lopinavir, ritonavir and nelfinavir. The compounds of this invention are inhibitors of HIV integrase and inhibitors of HIV replication. The inhibition of integrase *in vitro* and HIV replication in cells is a direct result of inhibiting the strand transfer reaction catalyzed by the recombinant integrase *in vitro* in HIV infected cells.

The compounds of the present invention specifically inhibit HIV integrase and HIV

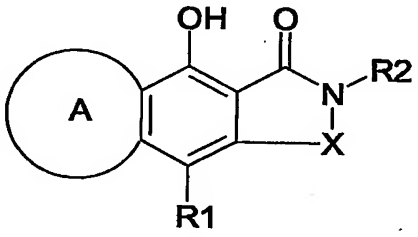
replication and not only are they active against wild-type HIV virus, but they also show activity against various mutant HIV viruses.

Other HIV integrase inhibitors are known in the art. For instance, WO0255079, WO0230931, WO0230930 and WO0230426 (all by Merck & Co., Inc.) disclose aza- and polyaza-naphthalenyl carboxamides useful as inhibitors of HIV integrase. WO0236734 (by Merck & Co., Inc.) discloses additionally aza- and polyaza-naphthalenyl ketones useful as inhibitors of HIV integrase.

CS225002 (by Krepelka Jiri and Vlckova Drahuse) discloses 9-phenyl-1H-benzo[f]isoindole-1,3-dione derivatives capable of inhibiting tumors in mice and rats. Similarly, CS210880 (by Krepelka Jiri, Vancurova Iva and Roubik Jiri) discloses certain 4-arylnaphthalene-2,3-dicarboxylic acid imides as antineoplastic active compounds.

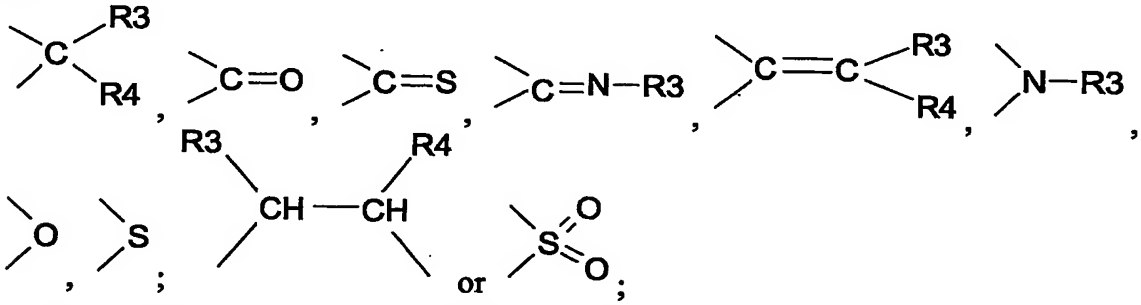
The article by Krepelka et al., Collect. Czech. Chem. Commun. (1982), 47(1), pp304-14 discloses the synthesis and neoplastic effects of some N-substituted imides of 1-substituted 4-arylnaphthalene-2,3-dicarboxylic acids.

The present invention concerns novel compounds as HIV integrase inhibitors, having the formula (I),



and their N-oxides, salts, stereoisomeric forms, racemic mixtures, prodrugs, esters and metabolites thereof, wherein

X is



A, also mentioned as "A-ring", together with the two carbons of the phenyl ring to which it is attached forms a monocyclic aryl or a monocyclic Het^2;

R^1 is hydrogen, halogen, nitro, cyano, sultam, sultim, C_{3-7}cycloalkyl, $C(=O)$-R^5, $S(=O)_y$-R^6, OR^7, NR^8R^9, $C(=NR^8)$-R^5, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^5, $S(=O)_y$-R^6, OR^7, and NR^8R^9;

R^2 is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^5, $S(=O)_y$-R^6, OR^7, NR^8R^9, $C(=NR^8)$-R^5, or optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^5, $S(=O)_y$-R^6, OR^7, and NR^8R^9;

R^3 is hydrogen, halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, $C(=O)$-R^5, $S(=O)_y$-R^6, OR^7, NR^8R^9, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, $C(=O)$-R^5, OR^7, and NR^8R^9;

R^4 is hydrogen, halogen, nitro, cyano, C_{3-7}cycloalkyl or C_{1-6}alkyl;

y represents an integer being zero, one or two;

R^5 is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^{10}, OR^{12}, NR^8R^{13}, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^{10}, $S(=O)_y$-R^{11}, OR^{12}, and NR^8R^{13};

R^6 is hydrogen, aryl, C_{3-7}cycloalkyl, Het^1, Het^2, OR^{12}, NR^8R^{13}, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^{10}, $S(=O)_y$-R^{11}, OR^{12}, and NR^8R^{13};

R^7 is hydrogen, aryl, C_{3-7}cycloalkyl, Het^1, Het^2, $C(=O)$-R^{10}, $S(=O)_y$-R^{11}, or optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano,C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^{10}, $S(=O)_y$-R^{11}, OR^{12}, and NR^8R^{13};

R^8 is hydrogen, aryl, Het^1, Het^2, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl or polyhaloC_{1-6}alkyl;

R^9 is hydrogen, aryl, C_{3-7}cycloalkyl, Het^1, Het^2, $C(=O)$-R^{10}, $S(=O)_y$-R^{11}, $C(=NR^8)$-R^5, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or

optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano,C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^{10}, $S(=O)_y$-R^{11}, OR^{12} and NR^8R^{13};

R^{10} is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^8, $C(=O)$-OR^8, $C(=O)$-NR^8R^8, OR^8, O-$C(=O)$-R^8, O-$S(=O)_y$-R^8, $S(=O)_y$-R^8, NR^8R^8, NR^8-$C(=O)$-R^8, NR^8-$S(=O)_y$-R^8, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^8, $C(=O)$-OR^8, $C(=O)$-NR^8R^8, $S(=O)_y$-R^8, $S(=O)_y$-OR^8, $S(=O)_y$-NR^8R^8, OR^8, O-$C(=O)$-R^8, O-$S(=O)_y$-R^8, NR^8R^8, NR^8-$C(=O)$-R^8, and NR^8-$S(=O)_y$-R^8;

R^{11} is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, OR^8, O-$C(=O)$-R^8, O-$S(=O)_y$-R^8, NR^8R^8, NR^8-$C(=O)$-R^8, NR^8-$S(=O)_y$-R^8, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^8, $C(=O)$-OR^8, $C(=O)$-NR^8R^8, $S(=O)_y$-R^8, $S(=O)_y$-OR^8, $S(=O)_y$-NR^8R^8, OR^8, O-$C(=O)$-R^8, O-$S(=O)_y$-R^8, NR^8R^8, NR^8-$C(=O)$-R^8, and NR^8-$S(=O)_y$-R^8;

R^{12} is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^8, $C(=O)$-OR^8, $C(=O)$-NR^8R^8, $S(=O)_y$-R^8, $S(=O)_y$-OR^8, $S(=O)_y$-NR^8R^8, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^8, $C(=O)$-OR^8, $C(=O)$-NR^8R^8, $S(=O)_y$-R^8, $S(=O)_y$-OR^8, $S(=O)_y$-NR^8R^8, OR^8, O-$C(=O)$-R^8, O-$S(=O)_y$-R^8, NR^8R^8, NR^8-$C(=O)$-R^8, and NR^8-$S(=O)_y$-R^8;

R^{13} is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^8, $C(=O)$-OR^8, $C(=O)$-NR^8R^8, $S(=O)_y$-R^8, $S(=O)_y$-OR^8, $S(=O)_y$-NR^8R^8, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^8, $C(=O)$-OR^8, $C(=O)$-NR^8R^8, $S(=O)_y$-R^8, $S(=O)_y$-OR^8, $S(=O)_y$-NR^8R^8, OR^8, O-$C(=O)$-R^8, O-$S(=O)_y$-R^8, NR^8R^8, NR^8-$C(=O)$-R^8, and NR^8-$S(=O)_y$-R^8;

R^{14} is hydrogen, phenyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl;

aryl as a group or part of a group represents a monocyclic or polycyclic aromatic or a partially saturated monocyclic or polycyclic carbocycles wherein any such carbocycle within the meaning of aryl may have up to 14 carbon atoms and may be optionally substituted with one or more substituents independently selected from

halogen, nitro, oxo, cyano, C_{3-7}cycloalkyl, Het^1, Het^2, $C(=O)$-R^8, $S(=O)_y$-R^{14}, OR^{14}, $NR^{14}R^{14}$, NR^{14}-O-$C(=O)$-R^{14}, NR^{14}-C_{1-6}alkanediyl-NR^{14}-Het^1, NR^{14}-C_{1-6}alkanediyl-NR^{14}-Het^2, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl, optionally polysubstituted C_{2-6}alkynyl and optionally polysubstituted phenyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, phenyl, $C(=O)$-R^{14}, OR^{14}, Het^1, Het^2, $C(=O)$-Het^1, $C(=O)$-Het^2, and $NR^{14}R^{14}$; and whereby the optional substituents on phenyl are each independently selected from halogen, hydroxy, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, O-C_{1-6}alkyl, and C_{1-6}alkanediyl-$NR^{14}R^{14}$;

Het^1 as a group or part of a group represents a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle having 3 to 14 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen and sulfur, and which may be optionally substituted on a carbon atom or where possible a nitrogen atom with one or more substituents independently selected from halogen, nitro, oxo, cyano, C_{3-7}cycloalkyl, $C(=O)$-R^{14}, $S(=O)_y$-R^{14}, OR^{14}, $NR^{14}R^{14}$, NR^{14}-O-$C(=O)$-R^{14}, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl, optionally polysubstituted C_{2-6}alkynyl and optionally polysubstituted phenyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, phenyl, $C(=O)$-R^{14}, OR^{14}, and $NR^{14}R^{14}$; and whereby the optional substituents on phenyl are each independently selected from halogen, hydroxy, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, O-C_{1-6}alkyl, and C_{1-6}alkanediyl-$NR^{14}R^{14}$;

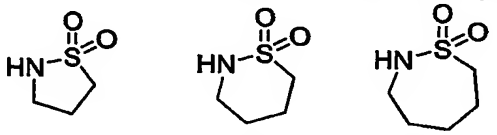
Het^2 as a group or part of a group represents an aromatic monocyclic, bicyclic or tricyclic heterocycle having 5 to 14 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen and sulfur, and which may be optionally substituted on a carbon atom or where possible a nitrogen atom with one or more substituents independently selected from halogen, nitro, oxo, cyano, C_{3-7}cycloalkyl, $C(=O)$-R^{14}, $S(=O)_y$-R^{14}, OR^{14}, $NR^{14}R^{14}$, NR^{14}-O-$C(=O)$-R^{14}, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl, optionally polysubstituted C_{2-6}alkynyl and optionally polysubstituted phenyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, phenyl, $C(=O)$-R^{14}, OR^{14}, and $NR^{14}R^{14}$; and whereby the optional substituents on phenyl are each independently selected from halogen, hydroxy, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, O-C_{1-6}alkyl, and C_{1-6}alkanediyl-$NR^{14}R^{14}$.

This invention also concerns the quaternization of the nitrogen atoms of the present compounds. A basic nitrogen can be quaternized with any agent known to those of

ordinary skill in the art including, for instance, lower alkyl halides, dialkyl sulfates, long chain halides and arylalkyl halides.

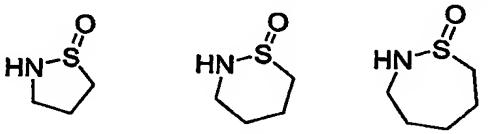
As used herein, the term "halo" or "halogen" as a group or part of a group is generic for fluoro, chloro, bromo or iodo.

The term sultam defines a cyclic aminosulfonyl group. Examples of a sultam are



and they may be attached to the remainder of the molecule via the nitrogen atom or a carbon atom.

The term sultim defines a cyclic aminosulfoxyl group. Examples of a sultim are



and they may be attached to the remainder of the molecule via the nitrogen atom or a carbon atom.

The term "C_{1-2}alkyl" is generic to methyl or ethyl.

The term "C_{1-3}alkyl" as a group or part of a group defines saturated hydrocarbon radicals having from 1 to 3 carbon atoms, such as the groups defined for C_{1-2}alkyl, propyl, isopropyl, and the like.

The term "C_{1-4}alkyl" as a group or part of a group defines straight and branched chained saturated hydrocarbon radicals having from 1 to 4 carbon atoms, such as the groups defined for C_{1-3}alkyl, butyl, 2-methyl-propyl, and the like.

The term "C_{2-4}alkyl" as a group or part of a group defines straight and branched chained saturated hydrocarbon radicals having from 2 to 4 carbon atoms, such as, for example, ethyl, propyl, butyl, 2-methyl-propyl, and the like.

The term "C_{1-6}alkyl" as a group or part of a group defines straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms. Examples of C_{1-6}alkyl are the groups defined for C_{1-4}alkyl, pentyl, hexyl, 2-methylbutyl, 3-methylpentyl, and the like.

The term "C_{2-6}alkyl" as a group or part of a group defines straight and branched chained saturated hydrocarbon radicals having from 2 to 6 carbon atoms, such as the groups defined for C_{2-4}alkyl, pentyl, hexyl, 2-methylbutyl, 3-methylpentyl, and the like.

The term "C_{1-2}alkanediyl" is generic to methanediyl, 1,2-ethanediyl, or 1,1-ethanediyl.

The term "C_{1-3}alkanediyl" as a group or part of a group defines bivalent hydrocarbons having from 1 to 3 carbon atoms, such as the groups defined for C_{1-2}alkanediyl, 1,3-propanediyl, and the like.

The term "C_{1-4}alkanediyl" as a group or part of a group defines bivalent straight and branched chained hydrocarbons having from 1 to 4 carbon atoms, such as the groups defined for C_{1-3}alkanediyl, 1,3-butanediyl, 1,4-butanediyl, and the like.

The term "C_{1-6}alkanediyl" as a group or part of a group defines bivalent straight and branched chained hydrocarbons having from 1 to 6 carbon atoms, such as the groups defined for C_{1-4}alkanediyl, 1,3-pentanediyl, 1,5-pentanediyl, 1,4-hexanediyl, 1,6-hexanediyl, and the like.

The term "C_{2-4}alkanediyl" as a group or part of a group defines bivalent straight and branched chained hydrocarbons having from 2 to 4 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,3-butanenediyl, 1,4-butanediyl, and the like.

The term "C_{2-6}alkanediyl" as a group or part of a group defines bivalent straight and branched chained hydrocarbons having from 2 to 6 carbon atoms, such as the groups defined for C_{2-4}alkanediyl, 1,3-pentanediyl, 1,5-pentanediyl, 1,4-hexanediyl, 1,6-hexanediyl, and the like.

The term "C_{2-3}alkenyl" as a group or part of a group defines hydrocarbon radicals having 2 or 3 carbon atoms containing at least one double bond such as, for example, ethenyl, propenyl, and the like.

The term "C_{2-5}alkenyl" as a group or part of a group defines hydrocarbon radicals having from 2 to 5 carbon atoms containing at least one double bond such as the groups defined for C_{2-3}alkenyl, butenyl, pentenyl and the like.

The term "C_{2-6}alkenyl" as a group or part of a group defines straight and branched chained hydrocarbon radicals having from 2 to 6 carbon atoms containing at least one double bond such as the groups defined for C_{2-5}alkenyl, hexenyl and the like.

The term "C_{2-5}alkenediyl" as a group or part of a group defines bivalent straight and branched chained hydrocarbons having from 2 to 5 carbon atoms containing at least one double bond such as, for example, 1,2-ethenediyl, 1,3-propenediyl, 1,3-butenediyl, 1,4-butenediyl, 1,2-pentenediyl, 1,5-pentenediyl and the like.

The term "C_{2-6}alkenediyl" as a group or part of a group defines bivalent straight and branched chained hydrocarbons having from 2 to 6 carbon atoms containing at least one double bond such as the groups defined for C_{2-5}alkenediyl, 1,4-hexenediyl, 1,6-hexenediyl, and the like.

The term "C_{2-3}alkynyl" as a group or part of a group defines hydrocarbon radicals having 2 or 3 carbon atoms containing at least one triple bond such as, for example, ethynyl, propynyl and the like.

The term "C_{2-5}alkynyl" as a group or part of a group defines straight and branched chained hydrocarbon radicals having from 2 to 5 carbon atoms containing at least one triple bond such as the groups defined for C_{2-3}alkynyl, butynyl, pentynyl and the like.

The term "C_{2-6}alkynyl" as a group or part of a group defines straight and branched chained hydrocarbon radicals having from 2 to 6 carbon atoms containing at least one triple bond such as the groups defined for C_{2-5}alkynyl, hexynyl and the like.

The term "C_{2-5}alkynydiyl" as a group or part of a group defines bivalent straight and branched chained hydrocarbons having from 2 to 5 carbon atoms containing at least one triple bond such as, for example, 1,2-ethynydiyl, 1,3-propynydiyl, 1,3-butynydiyl, 1,4-butynydiyl, 1,4-pentynydiyl, 1,5-pentynydiyl and the like.

The term "polyhaloC_{1-4}alkyl" as a group or part of a group, defines a C_{1-4}alkyl radical having the meaning as defined above wherein one or more hydrogen atoms are replaced with a halogen, preferably a bromo, chloro or fluoro atom. The term "polyhaloC_{1-4}alkyl" is also equivalent to the expression "C_{1-4}alkyl optionally substituted with one or more substituents independently selected from halogen". Examples of such polyhaloC_{1-4}alkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like.

The term "polyfluoroC_{1-4}alkyl" as a group or part of a group, defines a C_{1-4}alkyl radical having the meaning as defined above wherein one or more hydrogen atoms are replaced with a fluoro atom.

The term "polyhaloC_{1-6}alkyl" as a group or part of a group, defines a C_{1-6}alkyl radical

having the meaning as defined above wherein one or more hydrogen atoms are replaced with a halogen, preferably a bromo, chloro or fluoro atom. The term "polyhaloC_{1-6}alkyl" is also equivalent to the expression "C_{1-6}alkyl optionally substituted with one or more substituents independently selected from halogen". Examples of such polyhaloC_{1-6}alkyl radicals include the groups defined for 3-fluoropentyl, 2-chloro-6-bromohexyl, and the like.

The term "polyfluoroC_{1-6}alkyl" as a group or part of a group, defines a C_{1-6}alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a fluoro atom.

The term "C_{3-6}cycloalkyl" as a group or part of a group is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

The term "C_{3-7}cycloalkyl" as a group or part of a group is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl.

Examples of aryl include phenyl and naphtyl, or 1,2,3,4-tetrahydro-naphthalene, 1,2-dihydro-naphthalene, naphthalene, indan, 1H-indene, bicyclo[4.2.0]octa1,3,5-triene, 6,7,8,9-tetrahydro-5H-benzocycloheptene, 6,7-dihydro-5H-benzocycloheptene.

Whenever the terms "polysubstituted" and "one or more substituents" are used in defining the compounds of the present invention, unless otherwise stated, it is meant to indicate that one or more hydrogens on the atom indicated in the expression using "polysubstituted" and "one or more substituents" is replaced with a selection from the indicated group, provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic agent.

When any variable (e.g. halogen or C_{1-6}alkyl) occurs more than one time in any constituent, each definition is independent.

The term "prodrug" as used throughout this text means the pharmacologically acceptable derivatives such as esters, amides and phosphates, such that the resulting in vivo biotransformation product of the derivative is the active drug as defined in the compounds of the present invention. The reference by Goodman and Gilman (The Pharmacological Basis of Therapeutics, 8th ed, McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", pp13–15) describing prodrugs generally is hereby

incorporated. Prodrugs of a compound of the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy group, or an amino group is bonded to any group that, when the prodrug is administered to a patient, cleaves to form a free hydroxyl or free amino, respectively.

Prodrugs are characterized by excellent aqueous solubility, increased bioavailability and are readily metabolized into the active inhibitors in vivo.

For therapeutic use, the salts of the compounds of the present invention are those wherein the counter-ion is pharmaceutically or physiologically acceptable. However, salts having a pharmaceutically unacceptable counter-ion may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound of the present invention. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable or physiologically tolerable addition salt forms which the compounds of the present invention are able to form can conveniently be prepared using the appropriate acids, such as, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like acids.

Conversely said acid addition salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of the present invention containing an acidic proton may also be converted into their non-toxic metal or amine addition salt form by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, quaternary ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, N-methyl, -D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely said base addition salt forms can be converted by treatment with an appropriate acid into the free acid form.

The term "salts" also comprises the hydrates and the solvent addition forms that the compounds of the present invention are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The N-oxide forms of the present compounds are meant to comprise the compounds wherein one or several nitrogen atoms are oxidized to the so-called N-oxide.

The present compounds may also exist in their tautomeric forms. Such forms, although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

The term stereochemically isomeric forms of compounds of the present invention, as used hereinbefore, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of the present invention may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of the present invention both in pure form and in admixture with each other are intended to be embraced within the scope of the present invention.

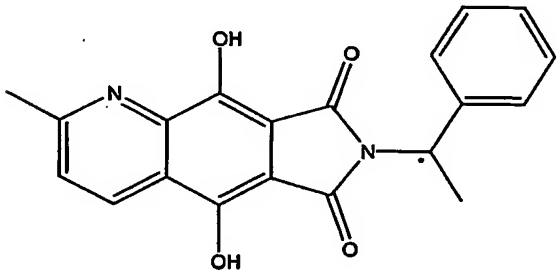
Pure stereoisomeric forms of the compounds and intermediates as mentioned herein are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure of said compounds or intermediates. In particular, the term 'stereoisomerically pure' concerns compounds or intermediates having a stereoisomeric excess of at least 80% (i. e. minimum 80% of one isomer and maximum 20% of the other possible isomers) up to a stereoisomeric excess of 100% (i.e. 100% of one isomer and none of the other), more in particular, compounds or intermediates having a stereoisomeric excess of 90% up to 100%, even more in particular having a stereoisomeric excess of 94% up to 100% and most in particular having a stereoisomeric excess of 97% up to 100%. The terms 'enantiomerically pure' and 'diastereomerically pure' should be understood in a similar way, but then having regard to the enantiomeric excess, respectively the diastereomeric excess of the mixture in question.

Pure stereoisomeric forms of the compounds and intermediates of this invention may be

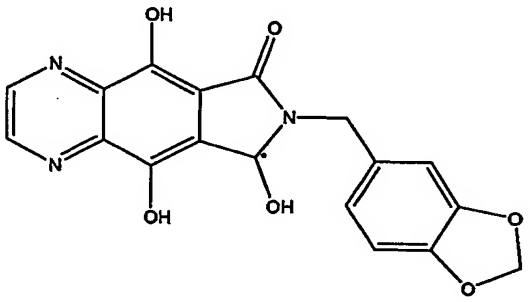
obtained by the application of art-known procedures. For instance, enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably, if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The diastereomeric racemates of compounds of the present invention can be obtained separately by conventional methods. Appropriate physical separation methods which may advantageously be employed are, for example, selective crystallization and chromatography, e.g. column chromatography.

The compounds may contain an asymmetric center and thus may exist as different stereoisomeric forms. Stereoisomeric forms may occur when for instance R^3 is different from R^4. Examples of asymmetric centers are indicated with an asterisk (*) in the structures below.



structure 1



structure 2

The absolute configuration of each asymmetric center that may be present in the compounds may be indicated by the stereochemical descriptors R and S, this R and S notation corresponding to the rules described in Pure Appl. Chem. 1976, 45, 11-30.

The present invention is also intended to include all isotopes of atoms occurring on the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

Interesting compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein A together with the two

carbons of the phenyl ring to which it is attached forms (i) a phenyl ring optionally substituted with one or more substituents independently selected from halogen, nitro, oxo, cyano, C_{3-7}cycloalkyl, Het^1, Het^2, $C(=O)$-R^8, $S(=O)_y$-R^{14}, OR^{14}, $NR^{14}R^{14}$, NR^{14}-O-$C(=O)$-R^{14}, NR^{14}-C_{1-6}alkanediyl-NR^{14}-Het^1, NR^{14}-C_{1-6}alkanediyl-NR^{14}-Het^2, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl, optionally polysubstituted C_{2-6}alkynyl and optionally polysubstituted phenyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, phenyl, $C(=O)$-R^{14}, OR^{14}, Het^1, Het^2, $C(=O)$-Het^1, $C(=O)$-Het^2, and $NR^{14}R^{14}$; and whereby the optional substituents on phenyl are each independently selected from halogen, hydroxy, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, O-C_{1-6}alkyl, and C_{1-6}alkanediyl-$NR^{14}R^{14}$; or (ii) a 5 or 6-membered aromatic heterocycle consisting of at least two carbon atoms and one or two nitrogen atoms, which heterocycle may optionally be substituted on a carbon atom or where possible a nitrogen atom with one or more substituents independently selected from halogen, nitro, oxo, cyano, C_{3-7}cycloalkyl, $C(=O)$-R^{14}, $S(=O)_y$-R^{14}, OR^{14}, $NR^{14}R^{14}$, NR^{14}-O-$C(=O)$-R^{14}, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl, optionally polysubstituted C_{2-6}alkynyl and optionally polysubstituted phenyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, phenyl, $C(=O)$-R^{14}, OR^{14}, and $NR^{14}R^{14}$; and whereby the optional substituents on phenyl are each independently selected from halogen, hydroxy, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, O-C_{1-6}alkyl, and C_{1-6}alkanediyl-$NR^{14}R^{14}$.

Particularly interesting compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein A together with the two carbons of the phenyl ring to which it is attached forms (i) a phenyl ring optionally substituted with one substituent selected from halogen or optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl, optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, phenyl, $C(=O)$-R^{14}, OR^{14}, Het^1, Het^2, $C(=O)$-Het^1, $C(=O)$-Het^2, and $NR^{14}R^{14}$; or (ii) a pyridinyl, a imidazolyl or a pyrazinyl each of which heterocycle may optionally be substituted on a carbon atom or where possible a nitrogen atom with one substituent selected from halogen or optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl, optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, phenyl, $C(=O)$-R^{14}, OR^{14}, Het^1, Het^2, $C(=O)$-Het^1, $C(=O)$-Het^2, and $NR^{14}R^{14}$.

More particularly interesting compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein A together with the two carbons of the phenyl ring to which it is attached forms (i) a phenyl ring optionally substituted with one substituent selected from halogen or optionally substituted C_{1-6}alkyl; whereby the optional substituent on C_{1-6}alkyl is selected from phenyl or OR^{14}; or (ii) a pyridinyl or a pyrazinyl each of which heterocycle may optionally be substituted on a carbon atom with one substituent selected from halogen or optionally substituted C_{1-6}alkyl; whereby the optional substituent on C_{1-6}alkyl is selected from phenyl or OR^{14}; or (iii) an imidazolyl optionally substituted on a nitrogen atom with optionally substituted C_{1-6}alkyl; whereby the optional substituent on C_{1-6}alkyl is selected from phenyl or OR^{14}.

Another interesting group of compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein R^1 is $C(=O)$-R^5, $S(=O)_y$-R^6, OR^7, NR^8R^9, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^5, $S(=O)_y$-R^6, OR^7, and NR^8R^9.

Particularly interesting compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein R^1 is OR^7, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl or optionally substituted C_{2-6}alkynyl; whereby the optional substituent on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl is OR^7.

More particularly interesting compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein R^1 is OR^7.

Even more particularly interesting compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein R^1 is OR^7; whereby R^7 is hydrogen, $C(=O)$-R^{10}, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl or optionally substituted C_{2-6}alkynyl; whereby the optional substituent on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl is selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^{10}, $S(=O)_y$-R^{11}, OR^{12}, and NR^8R^{13}.

Yet even more particularly interesting compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein

R^1 is OR^7; whereby R^7 is hydrogen, $C(=O)$-R^{10}, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl or optionally substituted C_{2-6}alkynyl; whereby the optional substituent on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl is selected from C_{3-7}cycloalkyl, aryl, Het^1, Het^2, and preferably is aryl.

Another interesting group of compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein R^2 is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, or optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^5, $S(=O)_y$-R^6, OR^7, and NR^8R^9.

Particularly interesting compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein R^2 is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, or optionally substituted C_{1-6}alkyl; whereby the optional substituent on C_{1-6}alkyl is selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^5, $S(=O)_y$-R^6, OR^7, and NR^8R^9.

More particularly interesting compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein R^2 is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, or optionally substituted C_{1-6}alkyl; whereby the optional substituent on C_{1-6}alkyl is selected from C_{3-7}cycloalkyl, aryl, Het^1, Het^2, and preferably is C_{3-7}cycloalkyl, aryl, Het^1.

Another interesting group of compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein X is -C(=O)-.

Another interesting group of compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein R^5 or R^{10} is $C(=O)$-R^8, $C(=O)$-OR^8, $C(=O)$-NR^8R^8, OR^8, O-$C(=O)$-R^8, O-$S(=O)_y$-R^8, NR^8R^8, NR^8-$C(=O)$-R^8, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl; or both R^5 and R^{10} are $C(=O)$-R^8, $C(=O)$-OR^8, $C(=O)$-NR^8R^8, OR^8, O-$C(=O)$-R^8, O-$S(=O)_y$-R^8, NR^8R^8, NR^8-$C(=O)$-R^8, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl.

Particularly interesting compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein R^5 or R^{10} is

$C(=O)$-R^8, $C(=O)$-OR^8, $C(=O)$-NR^8R^8, OR^8, NR^8R^8, C_{1-6}alkyl; or both R^5 and R^{10} are $C(=O)$-R^8, $C(=O)$-OR^8, $C(=O)$-NR^8R^8, OR^8, NR^8R^8, C_{1-6}alkyl.

Another interesting group of compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein R^6 or R^{11} is aryl, OR^8, NR^8R^8, C_{1-6}alkyl; or both R^6 and R^{11} are aryl, OR^8, NR^8R^8, C_{1-6}alkyl.

Another interesting group of compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein R^7 or R^{12} is hydrogen, $C(=O)$-R^{10}, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl or optionally substituted C_{2-6}alkynyl; whereby the optional substituent on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl is selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^{10}, $S(=O)_y$-R^{11}, OR^{12}, and NR^8R^{13}; or both R^7 and R^{12} are hydrogen, $C(=O)$-R^{10}, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl or optionally substituted C_{2-6}alkynyl; whereby the optional substituent on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl is selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^{10}, $S(=O)_y$-R^{11}, OR^{12}, and NR^8R^{13}.

Particularly interesting compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein R^7 or R^{12} is hydrogen, $C(=O)$-R^{10}, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl or optionally substituted C_{2-6}alkynyl; whereby the optional substituent on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl is selected from C_{3-7}cycloalkyl, aryl, Het^1, Het^2, and preferably is aryl; or both R^7 and R^{12} are hydrogen, $C(=O)$-R^{10}, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl or optionally substituted C_{2-6}alkynyl; whereby the optional substituent on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl is selected from C_{3-7}cycloalkyl, aryl, Het^1, Het^2, and preferably is aryl.

Another interesting group of compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein R^{14} is hydrogen, phenyl, C_{1-6}alkyl, C_{3-7}cycloalkyl.

Another interesting group of compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein R^8 is hydrogen or C_{1-6}alkyl.

Another interesting group of compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein R^9 is hydrogen, aryl, Het^1, Het^2, $C(=O)$-R^{10}, optionally polysubstituted C_{1-6}alkyl; whereby

the optional substituents on C_{1-6}alkyl are each independently selected from halogen, nitro, cyano,C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^{10}, $S(=O)_y$-R^{11}, OR^{12} and NR^8R^{13}.

Particularly interesting compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein R^9 is hydrogen, aryl, $C(=O)$-R^{10}, optionally substituted C_{1-6}alkyl; whereby the optional substituent on C_{1-6}alkyl is selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^{10}, $S(=O)_y$-R^{11}, OR^{12} and NR^8R^{13}.

More particularly interesting compounds are those compounds of formula (I) or any subgroup thereof as defined herein or combination of such subgroups, wherein R^9 is hydrogen or C_{1-6}alkyl.

A special group of compounds are those compounds of formula (I) wherein

A together with the two carbons of the phenyl ring to which it is attached forms (i) a phenyl ring optionally substituted with one substituent selected from halogen or optionally substituted C_{1-6}alkyl; whereby the optional substituent on C_{1-6}alkyl is selected from phenyl or OR^{14}; or (ii) a pyridinyl or a pyrazinyl each of which heterocycle may optionally be substituted on a carbon atom with one substituent selected from halogen or optionally substituted C_{1-6}alkyl; whereby the optional substituent on C_{1-6}alkyl is selected from phenyl or OR^{14}; or (iii) an imidazolyl optionally substituted on a nitrogen atom with optionally substituted C_{1-6}alkyl; whereby the optional substituent on C_{1-6}alkyl is selected from phenyl or OR^{14};

R^1 is OR^7;

R^2 is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, or optionally substituted C_{1-6}alkyl; whereby the optional substituent on C_{1-6}alkyl is selected from C_{3-7}cycloalkyl, aryl, Het^1, Het^2, and preferably is C_{3-7}cycloalkyl, aryl, Het^1;

X is -C(=O)-;

R^7 is hydrogen, $C(=O)$-R^{10}, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl or optionally substituted C_{2-6}alkynyl; whereby the optional substituent on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl is selected from C_{3-7}cycloalkyl, aryl, Het^1, Het^2, and preferably is aryl;

R^{10} is $C(=O)$-R^8, $C(=O)$-OR^8, $C(=O)$-NR^8R^8, OR^8, NR^8R^8, C_{1-6}alkyl;

R^{14} is hydrogen, phenyl, C_{1-6}alkyl, C_{3-7}cycloalkyl.

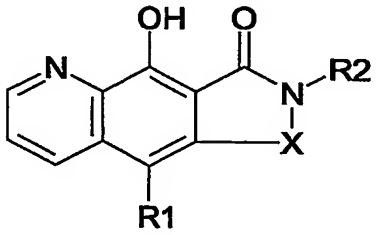
Suitably and where possible, any of the subgroups defined herein may be further restricted by

X is -C(=O)-;

R^1 is –OR^7;

R^2 is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, or optionally substituted C_{1-6}alkyl; whereby the optional substituent on C_{1-6}alkyl is selected from C_{3-7}cycloalkyl, aryl, Het^1, Het^2, and preferably is C_{3-7}cycloalkyl, aryl, Het^1.

A particular subgroup of the compounds of the present invention is defined by formula (IIa):



whereby

the pyridinyl ring may optionally be substituted with halogen or optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl, optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, phenyl, C(=O)-R^{14}, OR^{14}, Het^1, Het^2, C(=O)-Het^1, C(=O)-Het^2, and $NR^{14}R^{14}$.

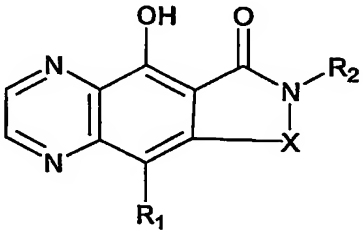
Suitably, the compounds of formula (IIa) may further be limited to those compounds wherein

X is -C(=O)-;

R^1 is $-OR^7$;

R^2 is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, or optionally substituted C_{1-6}alkyl; whereby the optional substituent on C_{1-6}alkyl is selected from C_{3-7}cycloalkyl, aryl, Het^1, Het^2, and preferably is C_{3-7}cycloalkyl, aryl, Het^1.

Another particular subgroup of the compounds of the present invention is defined by formula (IIb):



whereby the pyrazinyl ring may optionally be substituted with halogen or optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl, optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, phenyl, C(=O)-R^{14}, OR^{14}, Het^1, Het^2, C(=O)-Het^1, C(=O)-Het^2, and $NR^{14}R^{14}$.

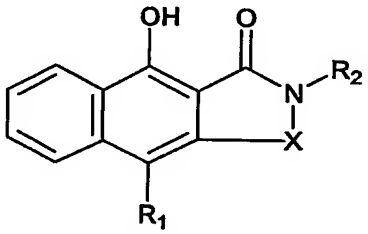
Suitably, the compounds of formula (IIb) may further be limited to those compounds wherein

X is -C(=O)-;

R^1 is $-OR^7$;

R^2 is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, or optionally substituted C_{1-6}alkyl; whereby the optional substituent on C_{1-6}alkyl is selected from C_{3-7}cycloalkyl, aryl, Het^1, Het^2, and preferably is C_{3-7}cycloalkyl, aryl, Het^1.

Another more particular subgroup of the compounds of the present invention is defined by formula (IIc):



whereby the phenyl ring may optionally be substituted with halogen or optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl, optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, phenyl, C(=O)-R^{14}, OR^{14}, Het^1, Het^2, C(=O)-Het^1, C(=O)-Het^2, and $NR^{14}R^{14}$.

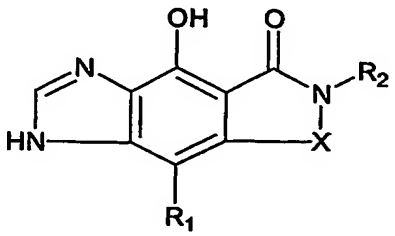
Suitably, the compounds of formula (IIc) may further be limited to those compounds wherein

X is -C(=O)-;

R^1 is $-OR^7$;

R^2 is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, or optionally substituted C_{1-6}alkyl; whereby the optional substituent on C_{1-6}alkyl is selected from C_{3-7}cycloalkyl, aryl, Het^1, Het^2, and preferably is C_{3-7}cycloalkyl, aryl, Het^1.

Another more particular subgroup of the compounds of the present invention is defined by formula (IId):



whereby the imidazolyl ring may optionally be substituted with halogen or optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl, optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, phenyl, C(=O)-R^{14}, OR^{14}, Het^1, Het^2, C(=O)-Het^1, C(=O)-Het^2, and $NR^{14}R^{14}$.

Suitably, the compounds of formula (IId) may further be limited to those compounds wherein

X is -C(=O)-;

R^1 is $-OR^7$;

R^2 is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, or optionally substituted C_{1-6}alkyl; whereby the optional substituent on C_{1-6}alkyl is selected from C_{3-7}cycloalkyl, aryl, Het^1, Het^2, and preferably is C_{3-7}cycloalkyl, aryl, Het^1.

The compounds of formula (IIa), (IIb), (IIc) and (IId) jointly form the compounds of formula (II).

An interesting subgroup within the definition of aryl are the fused bicyclic carbocycles in which one ring is a benzene ring and the other ring is saturated or unsaturated, with attachment via any carbon atom that results in a stable compound. Representative examples of this subset include 1,2,3,4-tetrahydro-naphthalene, 1,2-dihydro-naphthalene, naphthalene, indan, 1H-indene, bicyclo[4.2.0]octa-1,3,5-triene, 6,7,8,9-tetrahydro-5H-benzocycloheptene, 6,7-dihydro-5H-benzocycloheptene.

Another interesting subgroup within the definition of aryl are the fused tricyclic carbocycles in which one or two rings are a benzene ring and the other ring or rings are saturated or unsaturated, with attachment via any carbon atom that results in a stable compound. Representative examples include, 9H-fluorene, anthracene, 9,10-dihydro-anthracene, 2-phenyl-naphthalene, 2-phenyl-1,2,3,4-tetrahydro-naphthalene.

An interesting subgroup within the definition of Het^1 are those heterocycles having 5 to 10 ring members, preferably 5 to 8 ring members, more preferably 5 to 6 ring members.

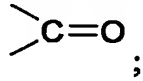
An interesting subgroup within the definition of Het^2 are those heterocycles having 5 to 10 ring members, preferably 5 to 6 ring members.

A particularly interesting subgroup within the definition of Het^1 and Het^2 is piperidinyl, piperazinyl, azepinyl, pyrrolyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolidinyl, triazolyl, tetrazolyl, imidazolinyl, pyridyl (also named pyridinyl),

pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinoxazolinyl, isothiazolidinyl, quinolinyl, pyrrolyl, thiazolyl, imidazolyl, isooxazolyl, thiadiazolyl, isoquinolinyl, benzimidazolyl, thiadazolyl, benzopyranyl, benzothiazolyl, benzoazolyl, furyl (also named furanyl), tetrahydrofuryl (also named tetrahydrofuranyl), tetrahydropuranyl, thienyl, benzothienyl, oxadiazolyl, and benzo-1,3-dioxacyclopentyl (also named 1,3-benzodioxolyl), tetrahydrothienyl, tetrahydrodioxothienyl, thiadiazinanyl, dioxothiadiazinanyl, thiazinanyl, dioxothiazinanyl, dioxothiazolidinyl, and isodioxothiazolidinyl, indolyl, benzotriazolyl, imidazo[4,5-b]pyridinyl, dihydroimidazo[4,5-b]pyridinyl, pyrazolo[4,3-c]pyridinyl, dihydropyrazolo[4,3-c]pyridinyl, tetrahydropyrazolo[4,3c]pyridinyl, pyrrolo[1,2-a]pyrazinyl, dihydropyrrolo[1,2-a]pyrazinyl, tetrahydropyrrolo[1,2-a]pyrazinyl, octahydropyrrolo[1,2-a]pyrazinyl, isoindolyl, indazolyl, indolinyl, isoindolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, chromanyl, isochromanyl, phthalazinyl, purinyl, 1,6-naphthyridinyl, 1,8-napthyridinyl, dihydroindolyl, dihydroisoindolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, imidazo[1, 2-a]pyrimidinyl, 2,3-dihydroimidazo[2,1-b][1, 3] thiazolyl, benzazepinyl, dihydrobenazepinyl, benzodiazepinyl, dihydrobenzodiazepinyl, and tetrahydrobenzodiazepinyl, phenothiazinyl, carbazolyl, beta-carbolinyl, tetrahydrobetacarbolinyl, acridinyl, phenazinyl, phenoxazinyl.

A particularly interesting subgroup within the definition of Het^1 and Het^2 is defined by a fused bicyclic Het^1 or Het^2 wherein one ring is a benzene ring and the other is a saturated or unsaturated heteroatom-containing ring, more in particular 3,4-dihydro-2H-benzo[1,4]oxazine, 2,3-dihydro-1H-benzoimidazole, 2,3-dihydro-1H-indole, 2,3-dihydro-1H-isoindole, 1H-indazole, benzooxazole, quinoline, isoquinoline, 4,5-dihydro-3H-benzo[b]azepine, 5H-benzo[e][1,4]diazepine, 2,5-dihydro-1H-benzo[b][1,4]diazepine, 2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine, 2,3,4,5-tetrahydro-1H-benzo[b]azepine.

A particular subgroup group of compounds are those compounds of formula (I) wherein one or more of the following restrictions apply:

X is  ; and/or

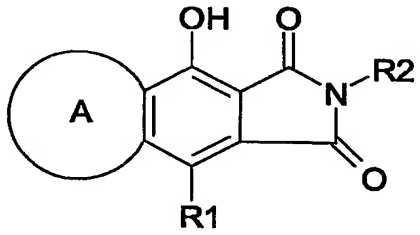
R^1 is hydroxy; O-C_{1-6}alkanediyl-aryl; O-C_{1-6}alkanediyl-cyano; O-C_{1-6}alkyl; O-C(=O)-C(=O)-O-C_{1-4}alkyl; and/or

R^2 is aryl, C_{3-7}cycloalkyl, Het^1, Het^2, C_{1-6}alkanediyl-C_{3-7}cycloalkyl, C_{1-6}alkanediyl-aryl, C_{1-6}alkanediyl-Het^1, C_{1-6}alkanediyl-Het^2, wherein the

C_{3-7}cycloalkyl, aryl, Het^1, or Het^2 may be optionally substituted on one or more carbons or heteroatoms with halogen, C_{1-4}alkyl, O-C_{1-4}alkyl, S(=O)$_2$-C_{1-4}alkyl, O-aryl; and/or

the A-ring may be unsubstituted or substituted on one or more carbons or heteroatoms with halogen, C_{1-4}alkyl, C_{1-4}alkanediyl-phenyl.

A more particular subgroup of the compounds of the present invention is defined by formula (III):



Suitably, the compounds of formula (III) may further be limited to those compounds wherein

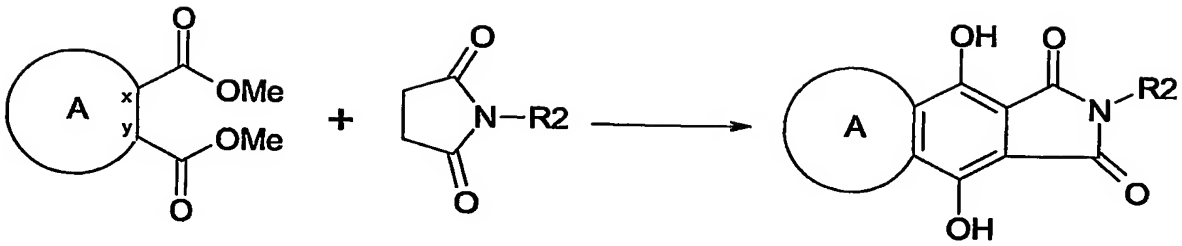
R^1 is $-OR^7$; more in particular hydroxy or O-C_{1-4}alkyl;

R^2 is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, or optionally substituted C_{1-6}alkyl; whereby the optional substituent on C_{1-6}alkyl is selected from C_{3-7}cycloalkyl, aryl, Het^1, Het^2, and preferably is C_{3-7}cycloalkyl, aryl, Het^1.

The compounds of the present invention can generally be prepared using procedures analogous to those procedures described in the examples.

Particular reaction procedures to make the present compounds are described below. In the preparations described below, the reaction products may be isolated from the medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, trituration and chromatography.

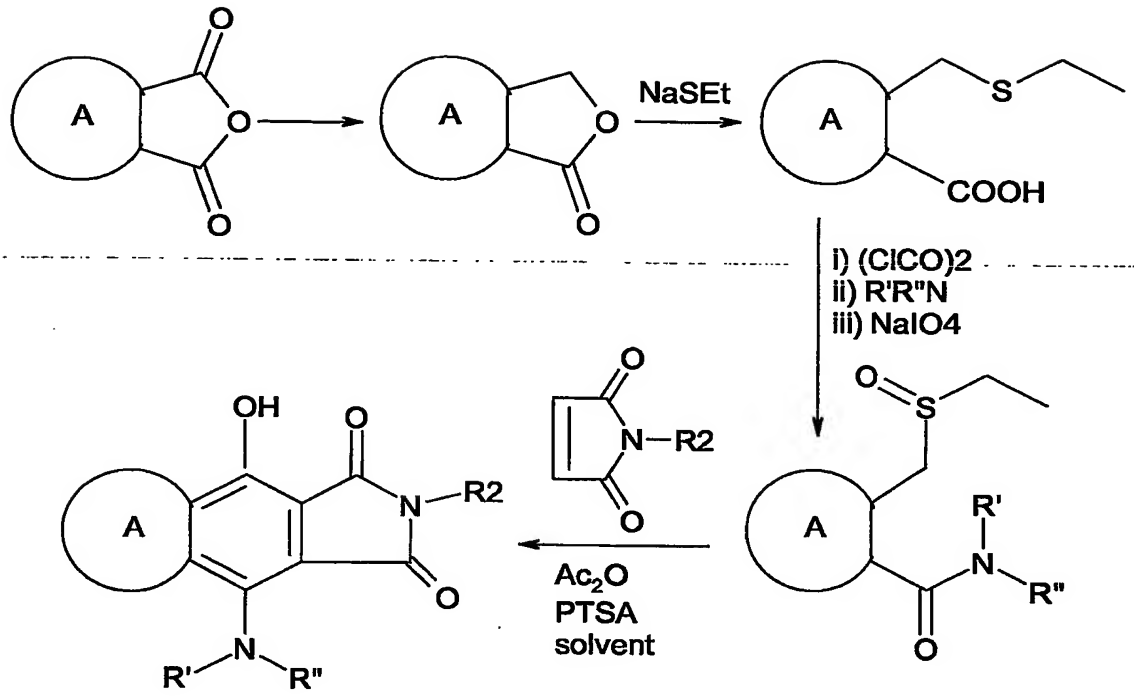
A strategy for a synthesis path of the compounds of the present invention is preparing on one hand a methyldicarboxylated A-ring, substituted on positions x and y, where y=x+1; preparing on the other hand, a N-R2 substituted succinimide; and reacting by means of a double Claisen condensation the methyldicarboxylated A-ring with the N-R2 substituted succinimide. The derived products may be optionally reduced, further substituted or experiment other reactions as required.



The x,y-methyldicarboxylated A-ring may be the esterification result of dissolving a x,y-aryldicarboxylic acid with an alcohol, catalyzed with mineral acids and heated. Sulfuric acid, hydrogen chloride, or other known catalysts may be employed as mineral acid catalysts. Alternatively, reacting a salt of x,y-aryldicarboxylate, e.g. sodium x,y-aryldicarboxylate with an haloalkane, in the presence of x,y-aryldicarboxylic acid and heating.

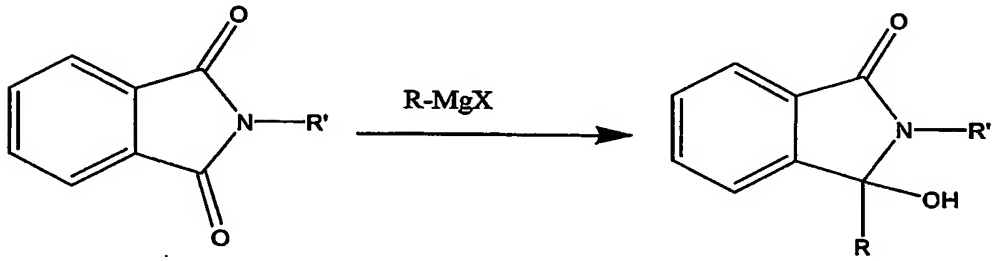
On a parallel scheme, the N-R2 substituted succinimide may be obtained by reacting a N-R2 substituted amine with succinic anhydride. Said reaction may be enhanced with the addition of suitable solvents, such as acetic acid, in the presence of catalysts like 4-dimethylaminopyridine (DMAP). Alternatively, products with solvent and nucleophilic catalyst functions could as well be employed, such as the pyridine-type solvents. N-R2 substituted succinimide are as well obtained by combining succinimides with haloalkyls, or haloalkanediyl-aryls in the presence of strong base and solvents.

A different strategy for a synthesis may for instance start from a A-ring fused with a cyclic anhydride, followed by a reduction to obtain a lactone, opening the lactone with a sodium thiolate, formation of an amide and oxidation of the sulfide into a sulfoxide with oxidizing agents such as sodium periodate, applying a Pummerer rearrangement, with subsequent Diels-Alder and elimination cascade in a one-pot-procedure to yield the compounds of this invention.

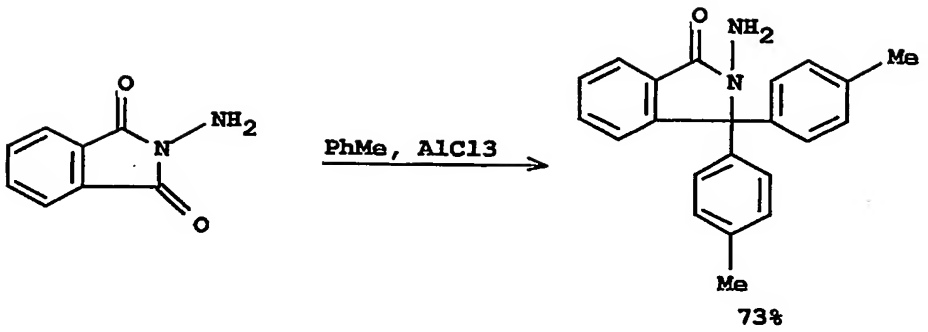


Reduction of the cyclic anhydride to obtain a lactone is achieved by treating with a reducing agent, optionally in the presence of an acid. Examples are available in the literature and include for instance reducing a quinolinic anhydride with $NaBH_4$ in the presence of AcOH to obtain a furopyridinone.

The derived products may be optionally reduced, further substituted or experiment other reactions. For instance, when X is an oxo group, such may be converted into dimethyl by following the synthesis encompassed in reference Tetrahedron, 57(13), 2581-2588; 2001. Optionally, the X=oxo group may be converted into 2 radicals: R and hydroxyl by means of a Grignard reaction, as here under illustrated:



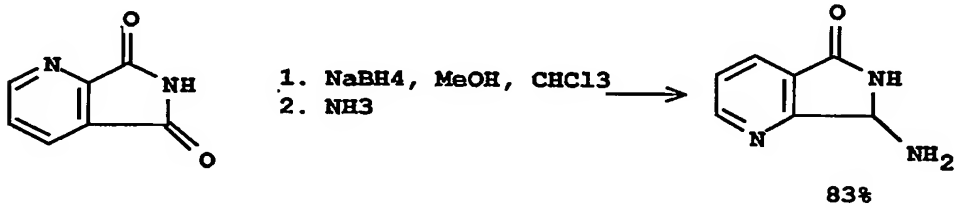
In addition, X as oxo group may be converted into a diphenyl moiety by reacting as here under illustrated:



Reference: Heterocycles, 46, 225-233; 1997;

Eventually the X=oxo moiety may be transformed into a thiooxo group through thionation with Lawesson's reagent (e.g. Synthesis 1996, 1485-1488).

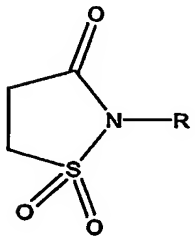
Conversion of the X=oxo group into an amino, may be performed as follows:



Reference: Bulletin of the Chemical Society of Japan, 60(11), 4178-80; 1987.

Further, by means of a Wittig reaction, an X=alkenediyl moiety is obtained from the oxo group.

Alternatively, one may obtain a ring closure through a double Claisen condensation on:



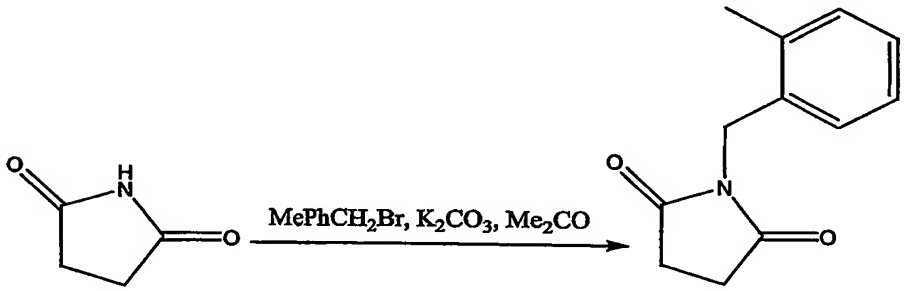
By reduction of the monothionated compound with Raney Nickel, one can obtain a X= –CH2- moiety.

Variants of the R1 group may be obtained as indicated below in the table:

target R1 moiety is	synthesis starting from the hydroxyl or amino group
hydrogen	by hydrogenating the triflate with Pd/C in a suitable solvent
halogen	by chlorinating the phenol with SOCl2 or POCl3
nitro	through nitration of the parent phenol.
sultam	by reacting the triflate or bromoderivative with 2H-1,2-Thiazine, tetrahydro-, 1,1-dioxide in the presence of a suitable copper catalyst.
C_{3-7}cycloalkyl	By a Heck reaction with a cycloalkene on the triflate followed by a hydrogenation
C(=O)-R	by a Diels Alder on the parent isobenzofurane system
$S(=O)_x$-R	by a Diels Alder on the parent isobenzofurane system
OR	by alkylation of the parent phenol. Already 1 example described
$C(=NR^8)$-R	by a Diels Alder on the parent isobenzofurane system
C_{1-6}alkyl	through a Stille coupling
C_{2-6}alkenyl	through a Stille coupling
C_{2-6}alkynyl	by a Sonogashira reaction

To introduce a m-halobenzyl as a R2 moiety, N-benzylmaleimide can be prepared by treating maleic anhydride with *m*-halobenzylamine to give N-halobenzylmaleamic acid, which is treated with anhydride NaOAc and anhydride HOAc at around 80°C.

To introduce C_{1-4}alkanediyl-aryl-C_{1-4}alkyl as a R2 moiety, one may follow the next reaction:

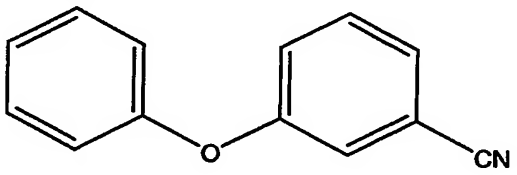


Alternatively, in the reaction above, reagent $MePhCH_2Br$ may include a Het^1 or Het^2 groups instead of the phenyl group, by which C_{1-4}alkanediyl-Het^1-C_{1-4}alkyl, and C_{1-4}alkanediyl-Het^2-C_{1-4}alkyl could be inserted as R2 moieties.

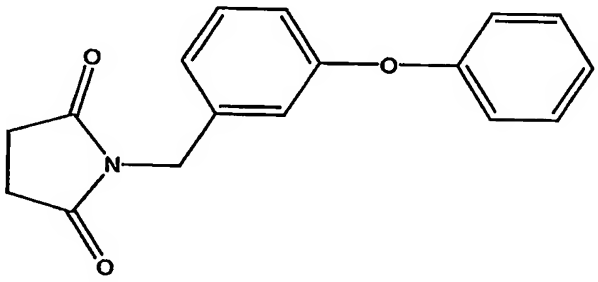
To introduce C_{3-7}cycloalkyl, or C_{1-4}alkanediyl-C_{3-7}cycloalkyl, as R2 moieties, as example, cyclohexylamine and maleic anhydride would be reacted at 100°C in O-xylene to give a slurry of N-cyclohexyl maleamic acid to which a slurry of

dicyclohexylamine salt of H_2SO_4 would be added and the mixture heated at 147°C for 2h with azeotropic H_2O removal to give N-cyclohexylmaleimide of high purity. Alternatively, N-cyclohexylmethylamine could be employed to obtain the corresponding N-cyclohexylmethyl)maleimide.

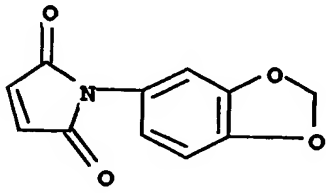
For the introduction of C_{1-4}alkanediyl-aryl-O-aryls as R2 moieties, the artisan may obtain those from commercially available compounds such as,



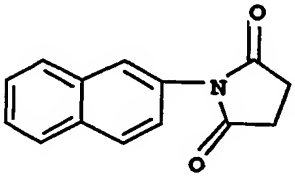
CAS 50789-45-2, available at Apin Chemical Ltd., and then convert them by a Raney-Nichel reaction into their amino equivalents, followed by a reaction with succinic anhydride to form:



Het[1] as R2 moiety, may be for instance obtained from commercial sources, such as Interchim Intermediates, CAS 170805-72-8:



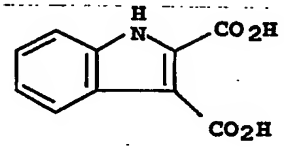
Het[2] as R2 moiety, may be for instance obtained from commercial sources, such as Interbioscreen Compound Library, CAS 69971-90-0:



Pyrazole, as A-ring, may be transformed into its corresponding maleic anhydride by placing 2-diazoketones in reaction with maleic anhydride and MeCOCHN2.

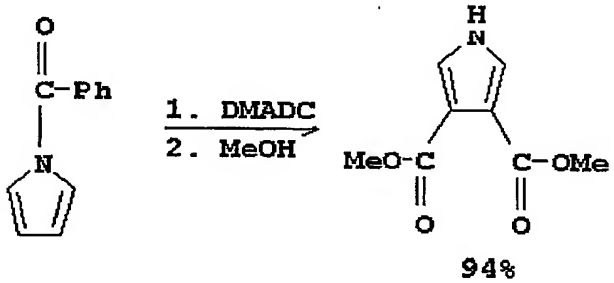
For preparation of 2,3-quinolinedicarboxylic acid, the artisan may follow the syntheis as disclosed in reference Bull. Soc. Chel. Belg., 89, nr. 3, 1980, pg 205, or alternatively in reference by OPPI, 14, 396, (82).

Indole with 2 carboxylic groups is commercially available from SALOR.

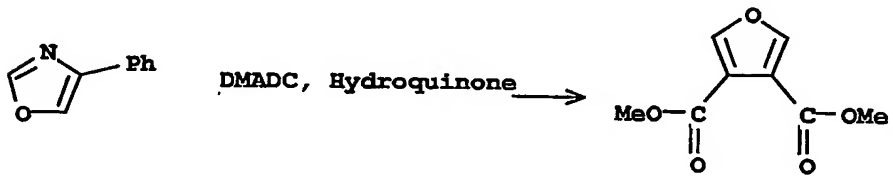


Synthesis of pyridazine-3,4-dicarboxylic acid may be achieved by a hetero Diels-Alder reaction as disclosed in Journal of Heterocylic Chemistry (1990), 27(3), 579-82.

Reactive pyrroles may be obtained as follows:

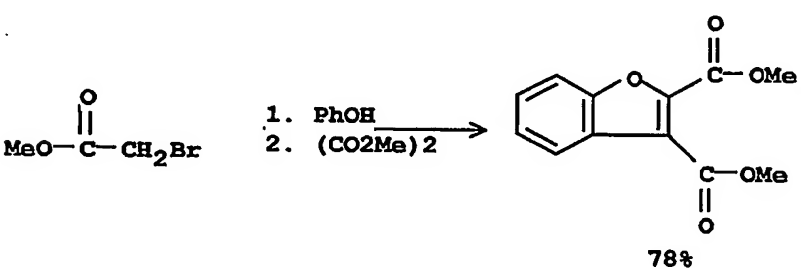


Similarly, reactive furane is obtained by:



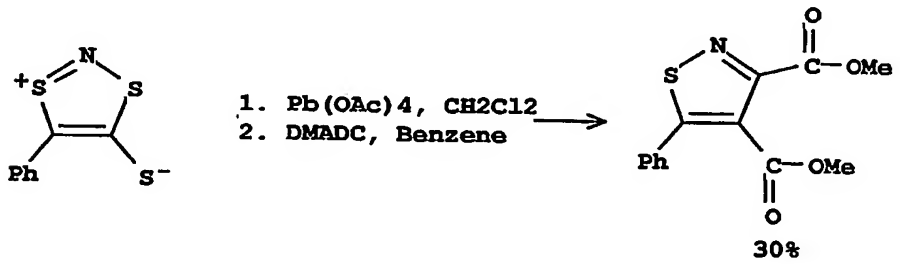
1H-1,2,3-Triazole-4,5-dicarboxylic acid, dimethyl is commercially available from ChemDiv, Inc. Product Library.

Reactive benzofurane is obtained for instance:

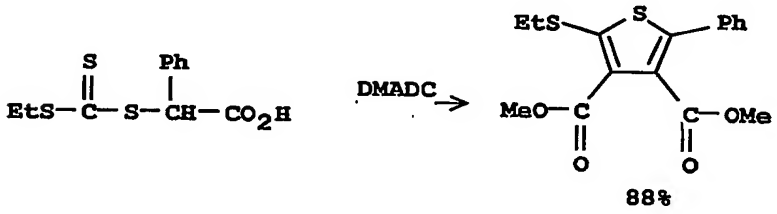


HCNO, prepared in situ by hydrolysis of Me2SiCNO in aqueous THF, may undergo cycloaddition reactions with alkenes and alkynes to give isoxazoles.

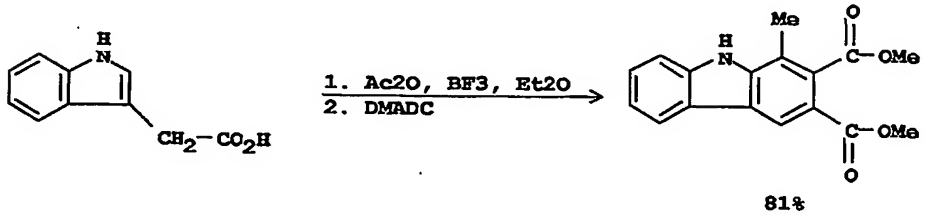
Isothiazole may become reactive with the introduction of the 2 carboxylate moieties as follows:



A thiophene with 2 carboxylate moieties may be obtained from:



A carbazole with 2 carboxylate groups is obtained from:



Reactive quinoxalines may be prepared as follows:

The compounds of the present invention may also be converted to the corresponding N-oxide forms following art-known procedures for converting a trivalent nitrogen into its N-oxide form. Said N-oxidation reaction may generally be carried out by reacting

the starting material of compounds with appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chloro-benzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. tert-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

The present compounds can thus be used in animals, preferably in mammals, and in particular in humans as pharmaceuticals per se, in mixtures with one another or in the form of pharmaceutical preparations.

Furthermore, the present invention relates to pharmaceutical preparations which as active constituents contain an effective dose of at least one of the compounds of this invention in addition to customary pharmaceutically innocuous excipients and auxiliaries. The pharmaceutical preparations normally contain 0.1 to 90% by weight of the compound. The pharmaceutical preparations can be prepared in a manner known per se to one of skill in the art. For this purpose, at least one of a compound of this invention, together with one or more solid or liquid pharmaceutical excipients and/or auxiliaries and, if desired, in combination with other pharmaceutical active compounds, are brought into a suitable administration form or dosage form which can then be used as a pharmaceutical in human medicine or veterinary medicine.

Pharmaceuticals which contain a compound according to the invention can be administered orally, parenterally, e.g., intravenously, rectally, by inhalation, or topically, the preferred administration being dependent on the individual case, e.g., the particular course of the disorder to be treated. Oral administration is preferred.

The person skilled in the art is familiar on the basis of his expert knowledge with the auxiliaries which are suitable for the desired pharmaceutical formulation. Beside solvents, gel-forming agents, suppository bases, tablet auxiliaries and other active compound carriers, antioxidants, dispersants, emulsifiers, antifoams, flavor corrigents, preservatives, solubilizers, agents for achieving a depot effect, buffer substances or colorants are also useful.

The compounds of the present invention are useful in the treatment of individuals infected by HIV and for the prophylaxis of these individuals. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals infected with viruses whose existence is mediated by, or depends upon, the integrase enzyme. Conditions which may be prevented or treated with the compounds of the present invention, especially conditions associated with HIV and other pathogenic retroviruses, include AIDS, AIDS-related complex (ARC), progressive generalized lymphadenopathy (PGL), as well as chronic CNS diseases caused by retroviruses, such as, for example HIV mediated dementia and multiple sclerosis.

The compounds of the present invention or any subgroup thereof may therefore be used as medicines against above-mentioned conditions. Said use as a medicine or method of treatment comprises the systemic administration to HIV-infected subjects of an amount effective to combat the conditions associated with HIV and other pathogenic retroviruses, such as HIV-1. Consequently, the compounds of the present invention can be used in the manufacture of a medicament useful for treating conditions associated with HIV and other pathogenic retroviruses.

In a preferred embodiment, the invention relates to the use of a compound of formula (I), (II) and (III) or any subgroup thereof in the manufacture of a medicament for treating or combating infection or disease associated with retrovirus infection in a mammal, such as HIV-1 infection. Thus, the invention also relates to a method of treating a retroviral infection, or a disease associated with retrovirus infection comprising administering to a mammal in need thereof an effective amount of a compound of formula (I), (II) and (III) or a subgroup thereof.

In another preferred embodiment, the present invention relates to the use of compound of this invention in the manufacture of a medicament for inhibiting a integrase of a retrovirus in a mammal infected with said retrovirus, in particular HIV-1 retrovirus.

In another preferred embodiment, the present invention relates to the use of compounds of this invention in the manufacture of a medicament for inhibiting retroviral integration, in particular HIV-1 integration.

The compounds of the present invention may also find use in inhibiting ex vivo samples containing HIV or expected to be exposed to HIV. Hence, the present compounds may be used to inhibit HIV present in a body fluid sample which contains or is suspected to contain or be exposed to HIV.

Also, the combination of an antiretroviral compound and a compound of the present invention can be used as a medicine. Thus, the present invention also relates to a product containing (a) a compound of the present invention, and (b) another antiretroviral compound, as a combined preparation for simultaneous, separate or sequential use in treatment of retroviral infections. Thus, to combat or treat HIV infections, or the infection and disease associated with HIV infections, such as Acquired Immunodeficiency Syndrome (AIDS) or AIDS Related Complex (ARC), the compounds of this invention may be co-administered in combination with for instance, binding inhibitors, such as, for example, dextran sulfate, suramine, polyanions, soluble CD4; fusion inhibitors, such as, for example, T20, T1249, SHC-C; co-receptor binding inhibitors, such as, for example, AMD 3100 (Bicyclams), TAK 779; RT inhibitors, such as, for example, foscarnet and prodrugs; nucleoside RTIs, such as, for example, AZT, 3TC, ddC, ddI, d4T, abacavir, FTC, DAPD, dOTC; nucleotide RTIs, such as, for example, PMEA, PMPA, tenofovir; NNRTIs, such as, for example, nevirapine, delavirdine, efavirenz, 8 and 9-Cl TIBO (tivirapine), loviride, TMC-125, TMC-120, MKC-442, UC 781, capravirine, DPC 961, DPC963, DPC082, DPC083, calanolide A, SJ-3366, TSAO, 4"-deaminated TSAO; RNAse H inhibitors, such as, for example, SP1093V, PD126338; TAT inhibitors, such as, for example, RO-5-3335, K12, K37; integrase inhibitors, such as, for example, L 708906, L 731988; protease inhibitors, such as, for example, amprenavir, ritonavir, nelfinavir, saquinavir, indinavir, lopinavir, lasinavir, BMS 232632, BMS 186316, DPC 681, DPC 684, tipranavir, AG1776, DMP 450, L 756425, PD178390, PNU 140135; glycosylation inhibitors, such as, for example, castanospermine, deoxynojirimycine.

The combination may provide a synergistic effect, whereby viral infectivity and its associated symptoms may be prevented, substantially reduced, or eliminated completely.

The compounds of the present invention may also be administered in combination with immunomodulators (e.g., bropirimine, anti-human alpha interferon antibody, IL-2, methionine enkephalin, interferon alpha, and naltrexone) or with antibiotics (e.g., pentamidine isothiorate) to ameliorate, combat, or eliminate HIV infection and its symptoms.

For an oral administration form, compounds of the present invention are mixed with suitable additives, such as excipients, stabilizers or inert diluents, and brought by means of the customary methods into the suitable administration forms, such as tablets, coated tablets, hard capsules, aqueous, alcoholic, or oily solutions. Examples of suitable inert

carriers are gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose, or starch, in particular, corn starch. In this case the preparation can be carried out both as dry and as moist granules. Suitable oily excipients or solvents are vegetable or animal oils, such as sunflower oil or cod liver oil. Suitable solvents for aqueous or alcoholic solutions are water, ethanol, sugar solutions, or mixtures thereof. Polyethylene glycols and polypropylene glycols are also useful as further auxiliaries for other administration forms.

For subcutaneous or intravenous administration, the active compounds, if desired with the substances customary therefor such as solubilizers, emulsifiers or further auxiliaries, are brought into solution, suspension, or emulsion. The compounds can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection or infusion preparations. Suitable solvents are, for example, water, physiological saline solution or alcohols, e.g. ethanol, propanol, glycerol, in addition also sugar solutions such as glucose or mannitol solutions, or alternatively mixtures of the various solvents mentioned.

Suitable pharmaceutical formulations for administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the compounds of the present invention, or their physiologically tolerable salts in a pharmaceutically acceptable solvent, such as ethanol or water, or a mixture of such solvents. If required, the formulation can also additionally contain other pharmaceutical auxiliaries such as surfactants, emulsifiers and stabilizers as well as a propellant. Such a preparation customarily contains the active compound in a concentration from approximately 0.1 to 50%, in particular from approximately 0.3 to 3% by weight.

In order to enhance the solubility and/or the stability of the compounds in pharmaceutical compositions, it can be advantageous to employ α-, β- or γ-cyclodextrins or their derivatives. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds in pharmaceutical compositions. In the preparation of aqueous compositions, addition salts of the subject compounds are obviously more suitable due to their increased water solubility.

Appropriate cyclodextrins are α-, β- or γ-cyclodextrins (CDs) or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6}alkyl-, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β-CD; hydroxyC_{1-6}alkyl-, particularly hydroxyethyl, hydroxypropyl or hydroxybutyl; carboxyC_{1-6}alkyl-, particularly carboxymethyl or carboxyethyl; C_{1-6}alkylcarbonyl-, particularly acetyl;

C_{1-6}alkyloxycarbonylC_{1-6}alkyl- or carboxyC_{1-6}alkyloxyC_{1-6}alkyl-, particularly carboxymethoxypropyl or carboxyethoxypropyl; C_{1-6}alkylcarbonyloxyC_{1-6}alkyl-, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β-CD, randomly methylated β-CD, 2,6-dimethyl-β-CD, 2-hydroxyethyl-β-CD, 2-hydroxyethyl-γ-CD, 2-hydroxypropyl-γ-CD and (2-carboxymethoxy)-propyl-β-CD, and in particular 2-hydroxypropyl-β-CD (2-HP-β-CD).

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxy-propyl and hydroxyethyl.

An interesting way of formulating the present compounds in combination with a cyclodextrin or a derivative thereof has been described in EP-A-721,331. Although the formulations described therein are with antifungal active ingredients, they are equally interesting for formulating the compounds of the present invention. The formulations described therein are particularly suitable for oral administration and comprise an antifungal as active ingredient, a sufficient amount of a cyclodextrin or a derivative thereof as a solubilizer, an aqueous acidic medium as bulk liquid carrier and an alcoholic co-solvent that greatly simplifies the preparation of the composition. Said formulations may also be rendered more palatable by adding pharmaceutically acceptable sweeteners and/or flavors.

Other convenient ways to enhance the solubility of the compounds of the present invention in pharmaceutical compositions are described in W0-94/05263, PCT application No. PCT/EP98/01773, EP-A-499299 and WO 97/44014, all incorporated herein by reference.

More in particular, the present compounds may be formulated in a pharmaceutical composition comprising a therapeutically effective amount of particles consisting of a solid dispersion comprising (a) a compound of the present invention, and (b) one or more pharmaceutically acceptable water-soluble polymers.

The term "a solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed more or less evenly throughout the other component or components. When said dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase as defined in thermodynamics, such a solid dispersion is referred to as "a solid solution". Solid

solutions are preferred physical systems because the components therein are usually readily bioavailable to the organisms to which they are administered.

The term "a solid dispersion" also comprises dispersions which are less homogenous throughout than solid solutions. Such dispersions are not chemically and physically uniform throughout or comprise more than one phase.

The water-soluble polymer in the particles is conveniently a polymer that has an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution.

Preferred water-soluble polymers are hydroxypropyl methylcelluloses or HPMC. HPMC having a methoxy degree of substitution from about 0.8 to about 2.5 and a hydroxypropyl molar substitution from about 0.05 to about 3.0 are generally water soluble. Methoxy degree of substitution refers to the average number of methyl ether groups present per anhydroglucose unit of the cellulose molecule. Hydroxypropyl molar substitution refers to the average number of moles of propylene oxide which have reacted with each anhydroglucose unit of the cellulose molecule.

The particles as defined hereinabove can be prepared by first preparing a solid dispersion of the components, and then optionally grinding or milling that dispersion. Various techniques exist for preparing solid dispersions including melt-extrusion, spray-drying and solution-evaporation.

It may further be convenient to formulate the present compounds in the form of nanoparticles which have a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than 1000 nm. Useful surface modifiers are believed to include those which physically adhere to the surface of the antiretroviral agent but do not chemically bond to the antiretroviral agent.

Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants.

Yet another interesting way of formulating the present compounds involves a pharmaceutical composition whereby the present compounds are incorporated in hydrophilic polymers and applying this mixture as a coat film over many small beads, thus yielding a composition with good bioavailability which can conveniently be

manufactured and which is suitable for preparing pharmaceutical dosage forms for oral administration.

Said beads comprise (a) a central, rounded or spherical core, (b) a coating film of a hydrophilic polymer and an antiretroviral agent and (c) a seal-coating polymer layer.

Materials suitable for use as cores in the beads are manifold, provided that said materials are pharmaceutically acceptable and have appropriate dimensions and firmness. Examples of such materials are polymers, inorganic substances, organic substances, and saccharides and derivatives thereof.

Another aspect of the present invention concerns a kit or container comprising a compound of the present invention, in an amount effective for use as a standard or reagent in a test or assay for determining the ability of a potential pharmaceutical to inhibit HIV integrase, HIV growth, or both. This aspect of the invention may find its use in pharmaceutical research programs.

The compounds of the present invention can be used in phenotypic resistance monitoring assays, such as known recombinant assays, in the clinical management of resistance developing diseases such as HIV. A particularly useful resistance monitoring system is a recombinant assay known as the Antivirogram™. The Antivirogram™ is a highly automated, high throughput, second generation, recombinant assay that can measure susceptibility, especially viral susceptibility, to the compounds of the present invention. (Hertogs K, de Bethune MP, Miller V et al. Antimicrob Agents Chemother, 1998; 42(2): 269-276, incorporated by reference).

The dose of the present compounds or of the physiologically tolerable salt(s) thereof to be administered depends on the individual case and, as customary, is to be adapted to the conditions of the individual case for an optimum effect. Thus it depends, of course, on the frequency of administration and on the potency and duration of action of the compounds employed in each case for therapy or prophylaxis, but also on the nature and severity of the infection and symptoms, and on the sex, age, weight and individual responsiveness of the human or animal to be treated and on whether the therapy is acute or prophylactic. Customarily, the daily dose of a compound of the present invention, in the case of administration to a patient approximately 75kg in weight is 1mg to 1g, preferably 3mg to 0.5g. The dose can be administered in the form of an individual dose, or divided into several, e.g. two, three, or four, individual doses.

The following table lists compounds of this invention, which were prepared following one of the above reaction schemes.

Table 1

Compound 1	7-Benzo[1,3]dioxol-5-ylmethyl-5,9-dihydroxy-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 2	7-(4-Fluoro-benzyl)-5,9-dihydroxy-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 3	5,9-Dihydroxy-7-(4-methyl-benzyl)-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 4	7-(4-Bromo-benzyl)-5,9-dihydroxy-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 5	7-Benzo[1,3]dioxol-5-ylmethyl-5,9-dihydroxy-pyrrolo[3,4-g]quinoline-6,8-dione
Compound 6	Oxalic acid 7-benzo[1,3]dioxol-5-ylmethyl-9-hydroxy-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoxalin-5-yl ester ethyl ester
Compound 7	5,9-Dihydroxy-7-(4-phenoxy-benzyl)-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 8	5,9-Dihydroxy-2-methyl-7-(1-phenyl-ethyl)-pyrrolo[3,4-g]quinoline-6,8-dione
Compound 9	2-Benzo[1,3]dioxol-5-yl-4,9-dihydroxy-benzo[f]isoindole-1,3-dione
Compound 10	7-Benzo[1,3]dioxol-5-yl-5,9-dihydroxy-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 11	2-(4-Fluoro-benzyl)-4,9-dihydroxy-benzo[f]isoindole-1,3-dione
Compound 12	4,9-Dihydroxy-2-phenethyl-benzo[f]isoindole-1,3-dione
Compound 13	5-Fluoro-2-(4-fluoro-benzyl)-4,9-dihydroxy-benzo[f]isoindole-1,3-dione
Compound 14	5,9-Dihydroxy-7-phenethyl-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 15	5,9-Dihydroxy-7-(1-phenyl-ethyl)-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 16	7-(3-Fluoro-benzyl)-5,9-dihydroxy-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 17	5,9-Dihydroxy-7-(4-methoxy-benzyl)-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 18	5,9-Dihydroxy-2-methyl-7-(1-phenyl-ethyl)-pyrrolo[3,4-g]quinoline-6,8-dione
Compound 19	5,9-Dihydroxy-2-methyl-7-phenethyl-pyrrolo[3,4-g]quinoline-6,8-dione
Compound 20	7-Benzo[1,3]dioxol-5-ylmethyl-5,9-dihydroxy-2-methyl-pyrrolo[3,4-g]quinoline-6,8-dione
Compound 21	7-(3-Fluoro-benzyl)-5,9-dihydroxy-2-methyl-pyrrolo[3,4-g]quinoline-6,8-dione
Compound 22	7-(4-Fluoro-benzyl)-5,9-dihydroxy-2-methyl-pyrrolo[3,4-g]quinoline-6,8-dione
Compound 23	5,9-Dihydroxy-7-(4-methoxy-benzyl)-2-methyl-pyrrolo[3,4-g]quinoline-6,8-dione
Compound 24	5,9-Dihydroxy-7-phenethyl-pyrrolo[3,4-g]quinoline-6,8-dione
Compound 25	5,9-Dihydroxy-7-(1-phenyl-ethyl)-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 26	7-Cyclohexylmethyl-5,9-dihydroxy-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 27	5,9-Dihydroxy-7-naphthalen-1-ylmethyl-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 28	5,9-Dihydroxy-7-(2-morpholin-4-yl-ethyl)-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 29	5,9-Dihydroxy-7-pyridin-4-ylmethyl-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 30	5,9-Dihydroxy-2-methyl-7-phenyl-pyrrolo[3,4-g]quinoline-6,8-dione
Compound 31	7-Benzo[1,3]dioxol-5-ylmethyl-5-benzyloxy-9-hydroxy-pyrrolo[3,4-g]quinoxaline-6,8-

	dione
Compound 32	7-Cyclopentyl-5,9-dihydroxy-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 33	7-(4-Fluoro-phenyl)-5,9-dihydroxy-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 34	5,9-Dihydroxy-7-(4-methanesulfonyl-benzyl)-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 35	7-(2-Bromo-phenyl)-5,9-dihydroxy-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 36	7-Benzo[1,3]dioxol-5-ylmethyl-5-hydroxy-9-prop-2-ynyloxy-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 37	7-Benzo[1,3]dioxol-5-ylmethyl-5-hydroxy-9-(3-methyl-butoxy)-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 38	6-Benzo[1,3]dioxol-5-ylmethyl-1-benzyl-4,8-dihydroxy-1H-1,3,6-triaza-s-indacene-5,7-dione
Compound 39	6-Benzo[1,3]dioxol-5-ylmethyl-4,8-dihydroxy-1H-1,3,6-triaza-s-indacene-5,7-dione
Compound 40	1-Benzyl-4,8-dihydroxy-6-(1-phenyl-ethyl)-1H-1,3,6-triaza-s-indacene-5,7-dione
Compound 41	7-Benzo[1,3]dioxol-5-ylmethyl-5-hydroxy-9-(3-phenyl-propoxy)-pyrrolo[3,4-g]quinoxaline-6,8-dione
Compound 42	4,9-Dihydroxy-2-(1-phenyl-ethyl)-benzo[f]isoindole-1,3-dione

EXAMPLE 1

Preparation of 7-Benzo[1,3]dioxol-5-ylmethyl-5,9-dihydroxy-pyrrolo[3,4-g]-quinoxaline-6,8-dione

Step 1: Preparation of 2,3-pyrazinemethyldicarboxylate

2,3-pyrazinedicarboxylicacid (21.9 g, 0.13 mol) was dissolved in MeOH (400 ml) and the pH was adjusted to 2 with HCl. This mixture was heated at reflux for 16 hrs. After evaporating MeOH, the residue was co-evaporated two times with toluene and dried in a vacuum oven to furnish 26.03 g 2,3-pyrazinemethyldicarboxylate.

MS: $[M+H]^+ = 197$

Step 2: Preparation of N-benzodioxol-5-ylsuccinimide

Piperonylamine (10.0 g, 0.07 mol), succinic anhydride (6.6 g, 0.07 mol) and a catalytic amount of DMAP were dissolved in HOAc (150 ml). The mixture was heated at reflux for 64 hrs. After evaporation of HOAc, the solid was dissolved in CH_2Cl_2 and washed with $NaHCO_3$ and diluted HCl. When the CH_2Cl_2 was removed, the residue was co-evaporated two times with toluene and dried in a vacuum oven to afford a light yellow raw material, which was used as such (13.35 g, 87%).

NMR: 1H ($CDCl_3$): 6.9 (s, 1H), 6.87 (d, J=7.8Hz, 1H), 6.71 (d, J=7.78Hz, 1H), 5.92 (s, 2H), 4.55 (s, 2H), 2.68 (s, 4H).

Step 3: Preparation of 7-Benzo[1,3]dioxol-5-ylmethyl-5,9-dihydroxy-pyrrolo[3,4-g]-quinoxaline-6,8-dione

2,3-pyrazinemethyldicarboxylate (398 mg, 2.03 mmol) and N-benzodioxol-5-ylsuccinimide (487 mg, 2.09 mmol) were dissolved in THF (40 ml). After NaH (4.92 mmol) and MeOH (3 drops) were carefully added, the suspension was heated at reflux for 16 hrs. When THF was evaporated, the residue was suspended in water and ether. The dark red heterogeneous mixture turns yellow after addition of HCl. This mixture was then vigorously stirred for several hrs. The yellow precipitate was then filtered, washed with some ether and dried in a vacuum oven (406 mg, 55%).

MS: $[M+H]^+ = 366$, $[M-H]^- = 364$

NMR: 1H (DMSO): 11.2 (br.s, 2H), 9.10 (s, 2H), 6.89 (d, J=1.5Hz, 1H), 6.87 (d, J=8Hz, 1H), 6.80 (dd, J=8Hz, J=1.5Hz, 1H), 5.97 (s, 2H), 4.64 (s, 2H).

EXAMPLE 2

Preparation of 5,9-Dihydroxy-2-methyl-7-phenethyl-pyrrolo[3,4-g]quinoline-6,8-dione

Step 1: Preparation of 6-methyl-2,3-pyridinemethyldicarboxylate

6-methyl-2,3-pyridinedicarboxylic acid (5.1 g, 0.03 mol) was dissolved in MeOH (80 ml) and the pH was adjusted to 2 with HCl/isopropanol 6N. This mixture was heated at reflux for 16 hrs. After evaporating MeOH, the residue was co-evaporated two times with toluene and dried in a vacuum oven to get a yellow solid (5.81g, 98.7%).

MS: $[M+H]^+ = 210$

Step 2: Preparation of N-phenethylsuccinimide

Phenethylamine (7.0 g, 0.06 mol), succinic anhydride (5.8 g, 0.06 mol) and a catalytic amount of DMAP were dissolved in HOAc (100 ml). Then it was heated at reflux for 64 hrs. After evaporation of HOAc, the solid was dissolved in CH_2Cl_2 and washed with $NaHCO_3$ and diluted HCl. The solution was dried with $MgSO_4$, evaporated and the residue was dried in a vacuum oven to afford 11.6g (98.7%), which was used as such.

Step 3: Preparation of 5,9-Dihydroxy-2-methyl-7-phenethyl-pyrrolo[3,4-g]quinoline-6,8-dione

6-methyl-2,3-pyridinemethyldicarboxylate (410 mg, 1.96 mmol) and N-phenethyl-succinimide (379 mg, 1.87 mmol) were dissolved in THF (40 ml). After NaH (4.60 mmol) and MeOH (4 drops) were carefully added, the suspension was heated at reflux for 16 hrs. When THF was evaporated, the residue was suspended in water and ether. The dark red heterogeneous mixture turns yellow after addition of HCl. This mixture

was then vigorously stirred for several hours. The yellow precipitate was then filtered, washed some ether and dried in a vacuum oven (265 mg, 41%).

MS: $[M+H]+ = 349$, $[M-H]- = 347$

NMR: 1H (DMSO): 10.60 (s, 1H), 8.57 (d, J=8.55Hz, 1H), 7.66 (d, J=8.55Hz, 1H), 7.35-7.15 (m, 5H), 3.79 (t, J=7.35Hz, 2H), 2.93 (t, J=7.35Hz, 2H), 2.75 (s, 3H).

EXAMPLE 3

Preparation of 6-Benzo[1,3]dioxol-5ylmethyl-4,8-dihydroxy-1H-1,3,6-triaza-s-indacene-5,7-dione

Step 1: Preparation of 1-Benzyl-1H-imidazole-4,5-dicarboxylic acid dimethyl ester

Imidazole-dicarboxylic acid dimethylester (5.1 g, 0.03 mol) was stirred in MeOH (150 ml). To this suspension, Na (680 mg, 0.03 mol) was added. When all solids were dissolved benzylbromide (4.8 g, 0.02 mol) was added, the mixture was heated at reflux for 16 hours. After evaporating MeOH, the residue was dissolved in CH_2Cl_2 and stirred with silica-gel. When the silica was removed by filtration and the solvent was evaporated, the solid was purified over a short silica column to afford the title compound (8.84g, 75.9%).

MS: $[M+H]+ = 275$

Step 2: Preparation of N-benzodioxol-5-ylsuccinimide

The same synthesis route was used as in step 2 of example 1.

Step 3: Preparation of 6-Benzo[1,3]dioxol-5ylmethyl-1-benzyl-4,8-dihydroxy-1H-1,3,6-triaza-s-indacene-5,7-dione

The compound from step 1 (725 mg, 2.65 mmol) and N-benzodioxol-5-ylmethyl-succinimide (616 mg, 2.64 mmol) were dissolved in THF. After NaH (8.00 mmol) and MeOH (4 drops) were carefully added, the suspension was heated at reflux for 16 hours. When THF was evaporated, the residue was suspended in water and ether. The dark red heterogeneous mixture turns yellow after addition of HCl pH = ± 5 to 6). This mixture was then vigorously stirred for several hours. The yellow precipitate was then filtered, washed with some ether and dried in a vacuum oven (1.15g, 98.1%).

MS: $[M+H]+ = 444$

Step 4: Preparation of 6-Benzo[1,3]dioxol-5ylmethyl-4,8-dihydroxy-1H-1,3,6-triaza-s-indacene-5,7-dione

A mixture of product obtained in Step 3 (0.88g , 2.60 mmol), 0.3g Pd/C (10%), 100ml MeOH and3ml Et3N was hydrogenated for 48 hours. After filtration and evaporation, the title compound was obtained (237 mg, 33%).

MS: $[M+H]+ = 354$, $[M-H]- = 352$

EXAMPLE 4

Preparation of 7-biphenyl-4-ylmethyl-5,9-dihydroxy-pyrrolo[3,4-g]quinoxaline-6,8-dione

Step 1: Preparation of 2,3-pyrazinemethyldicarboxylate

2,3-pyrazinedicarboxylicacid (21.9 g, 0.13 mol) was dissolved in MeOH (400 ml) and the pH was adjusted to 2 with HCl. This mixture was heated at reflux for 16 hours. After evaporating MeOH, the residue was co-evaporated two times with toluene and dried in a vacuum oven to furnish 26.03 g and used as such (yield quantitative).

MS: $[M+H]^+ = 197$ (low current)

Step 2: Synthesis of 4-phenyl-N-benzylsuccinimide

268 mg 4-Bromobenzylsuccinimide (1 mmol), 122 mg benzene boronic acid (1 mmol), 202 mg triethylamine (2 mmol) and 78.6 mg trans-dichlorobis(tri-o-tolylphosphine)-palladium (II) were added to 50 ml acetonitrile. After 3 nights refluxing, 60-65 % conversion was obtained, and was followed by evaporation and recrystallisation from ethylacetate/hexane, which was continued by filtration, dissolving in methylene chloride, and purification on silicagel. After evaporation an oil with 60-65 % purity (LCMS) was isolated. A 58.1 % yield was reached. The product was used in the next reaction step as such.

Step 3: Synthesis of 7-biphenyl-4-ylmethyl-5,9-dihydroxy-pyrrolo[3,4-g]quinoxaline-6,8-dione

642 mg 4-Phenylbenzyl-N-succinimide (2.43 mmol), 500 mg 2,3-pyrazinemethyl-dicarboxylate (2.55 mmol), 225 mg NaH 60 % in parafine oil (5.63 mmol) and 6 drops methanol were added to 20 ml THF. Refluxing was applied till all reagents had reacted (TLC Ethylacetate / Hexane: 70 / 30). Excess NaH was neutralised with water, 100ml in total, and was followed with the evaporation of THF. The aqueous solution was acidified with HCl 37 % till pH = 1. 50 ml diethylether was added and the mixture was shaken vigorously. The precipitate was filtered off, rinsed with diethylether and dried in a vacuum oven. The precipitate had a purity of 97.9 % by LCMS. A 18.8 % yield was reached.

MS: $[M+H]^+ = 398$, $[M-H]^- = 396$

EXAMPLE 5

Preparation of 7-Benzo[1,3]dioxol-5-ylmethyl-5-hydroxy-9-(3-methyl-butoxy)-pyrrolo[3,4-g]quinoxaline-6,8-dione

A solution of 7-Benzo[1,3]dioxol-5-ylmethyl-5,9-dihydroxy-pyrrolo[3,4-g]quinoxaline-6,8-dione (365 mg, 1.0 mmol), 1-Bromo-3-methylbutane (151 mg, 1.0 mmole),

potassium carbonate (138 mg, 1.0 mmole) in DMF was warmed at 100°C overnight. This solution was evaporated to dry, washed with water and the organic phase extracted with ethyl acetate. After drying on magnesium sulfate, filtration, evaporation of solvent, purification, 10 mg were isolated and analysed through LC/MS.

MS: $[M+H]^+ = 436$, $[M-H]^- = 434$.

ES-: 434,263,227.

ES+: 436, 366, 314, 244, 135.

EXAMPLE 6

Antiviral analyses

The compounds of the present invention were examined for anti-viral activity in a cellular assay. The assay demonstrated that these compounds exhibited potent anti-HIV activity against a wild type laboratory HIV strain (HIV-1 strain LAI, named as "IIIB") and a panel of mutant viruses with multi-drug resistance. The cellular assay was performed according to the following procedure:

HIV- or mock-infected MT4 cells equipped with a LTR-GFP reporter were incubated for three days in the presence of various concentrations of the inhibitor. At the end of the incubation period, the replicating virus in the control cultures had killed all HIV-infected cells in the absence of any inhibitor. The anti-viral replication assay is based on a GFP readout, and directly measures the ongoing replication of virus in MT4 cells via the specific interaction of HIV-tat with LTR-sequences coupled to GFP. The inhibitory activity of the compound was monitored on the virus-infected cells and was expressed as IC_{50}. This value represents the amount of the compound required to protect 50% of the cells from the cytopathogenic effect of the virus. The toxicity (Tox) of the compound was measured on the mock-infected cells and was expressed as CC_{50}, which represents the concentration of compound required to inhibit the growth of the cells by 50%. The toxicity assay is also based on GFP-readout, where a reduced expression of the GFP reporter protein serves as a marker for cellular toxicity of a compound. The selectivity index (SI) (ratio CC_{50}/IC_{50}) is an indication of the selectivity of the anti-HIV activity of the inhibitor.

Because of the increasing emergence of drug resistant HIV strains, the compounds were tested for their potency against different drug-resistant HIV-1 strains. Strains SM026, SM052, and T13299 are strains containing mutations that cause resistance against reverse transcriptase inhibitors. T13275 is a HIV-strain containing multi-drug (reverse transcriptase and protease) resistance mutations. SM026 (V003I, K103N, Y181C, E224D/E, P313P/S), SM052 (V003I, K101E, K103N), T13299 (V003I, L100I, K103N, E138G, V179I, Y181C, L214F, V276V/I, A327A/V), T13275 (V003I, L010F,

I013V, V032T, S037N, M046I, I047V, I050V, L063P, A071V, I084V, L089V, T091A, Q092R, K020R, E028K, M041L, K043E, E044A, D067N, L074I, K103N, V118I, D123N, S162C, Y181C, G196K, Q207E, L210W, R211K, L214F, T215Y, K219N, P225H, D250E, P272A, R277K, I293V, P294T, E297K, K311R, R358K, T376A, E399D, T400L).

Enzymatic integrase assay

The activity of HIV-integrase was determined using an oligonucleotide-based assay in which the DNA strand transfer by preformed complexes of integrase and processed DNA was measured by means of an enzyme-linked immunosorbent assay (ELISA) in microtiter plate format. Recombinant His-tagged HIV-1 integrase was produced in the E. *coli* strain BL21(DE3) from the plasmid pINSD.His.sol (available from NIH) after induction with isopropyl-β-D-thiogalactopyranoside (IPTG) according to described procedures (cfr. ref. Jenkins et al., "A soluble active mutant of HIV-1 integrase", J. Biol. Chem. 271 (1196), 7712-7718). HPLC-purified oligodeoxynucleotides were obtained from Proligo, and used for preparation of the viral DNA substrate and target DNA.

INb-1C: 5' - bGTGTGGAAAATCTCTAGCAGT - 3'
IN-1NC: 5' – ACTGCTAGAGATTTTCCACAC – 3'
INT5: 5' - TGACCAAGGGCTAATTCACTf - 3'
INT6: 5' – AGTGAATTAGCCCTTGGTCAf - 3'

INb-1C is 5'-biotinylated, INT5 and INT6 are at the 3'-end labeled with FITC. INb-1C and IN-1NC correspond to the U5 end of the HIV-1 LTR. The DNA substrate for the integrase reactions was made by annealing INb-1C and IN-1NC. An equimolar mixture of INb-1C and IN-1NC was heated shortly at 95°C in the presence of 100 mM NaCl and allowed to cool slowly to room temperature. In the same way, INT5 and INT6 were annealed to produce a target DNA molecule.

The integration strand transfer reactions were performed in the following way: 20 nM biotinylated DNA substrate INb-1C/IN-1NC was pre-incubated with 300 nM HIV-integrase at 37°C for 5 min, to allow the cleavage reaction to occur. The candidate compounds and 50 nM target DNA INT5/INT6 were added to the reaction mix containing 20 mM Hepes pH 7.5, 25 mM NaCl, 5 mM $MnCl_2$, 2 mM DTT, and 50 µg/ml BSA, and incubated for 2h at 37°C. The reaction mix was transferred to streptavidin-coated plates (Exiqon), which were prewashed (three times) with 5 x SSCT, and incubated for 1h at room temperature to allow capture of the biotinylated viral DNA/target DNA complex. Plates were washed three times with 2 x SSCT

buffer, and anti-FITC POD-coupled antibody (Roche) was added and incubated for 1h at room temperature to detect integrated FITC-labeled target DNA. After a final washing step with PBST (5 times), BM chemiluminescent POD-substrate (Roche) was added, and luminescence was read out.

The table below list the pIC_{50} values for those compounds tested in the enzymatic integrase assay. The pIC_{50} is expressed in Molar units and is the value according to the following formula:

$$pIC_{50} = 6 - \log IC_{50}$$

wherein the IC_{50} value is the drug concentration at which 50% of the enzyme or viral activity is inhibited, and is expressed in μMolar units.

Compound	pIC_{50}
1	6.21
3	5.8
2	6.38
4	6.66
21	6.06
22	6.40
18	5.12
19	5.38
20	5.67
8	4.97
26	5.66
17	6.25
6	5.50
24	5.60
27	5.85
14	5.69
16	6.25
7	5.31
30	4.62
23	5.83
15	5.98
31	<4.00
37	5.83
35	5.74
5	5.25
25	5.69
12	<4.00
42	<4.00
11	<4.00
13	<4.00
38	6.32
40	5.95
39	5.69
29	5.17
34	5.06
10	5.00
36	4.74
33	4.66
28	4.18
32	4.98

Time of addition assay

In a time-of-addition experiment, the step in the HIV replication cycle in which a compound is active was determined and compared with reference compounds including

inhibitors for binding/fusion, reverse transcriptase, integrase and protease. When a potent antiviral compound was added at the time of infection, no viral replication took place. But, if addition of compound was delayed, protection was observed up to the moment that the virus had passed the stage at which the inhibitor interacted. The use of reference compounds with a known mode of action was essential for the correct interpretation of the results.

MT4-LTR-EGFP cells were infected at a high multiplicity of infection (MOI) by centrifugation for 10 min at 1200 g. Unadsorbed virus was removed by two washing steps at 4°C in order to synchronize the infection. From 30 min post infection on, the compounds 1-43 were added to parallel cultures in microtiter plates at different times. The cultures were scored microscopically for fluorescence 24 hours after infection and supernatant was collected. HIV replication in the supernatant samples was quantified by measuring the concentration of the p24 viral antigen using a commercial kit, according to the manufacturer protocol (NEN). Because of the high MOI used in this type of experiments, concentrations of inhibitors were at least 100 fold higher than their EC_{50} value in the cellular antiviral assay. The score of the compounds 1-41 was integrase.

Analysis of HIV integration using real-time PCR

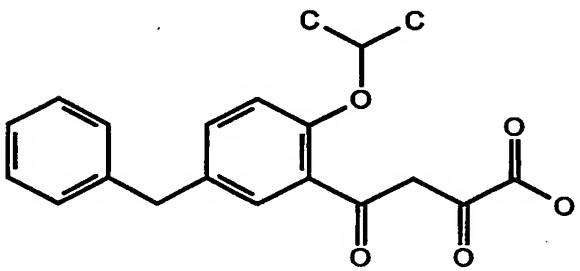
For confirmation that compounds inhibited the viral replication cycle at the integration step, DNA extracts of cells infected with HIV in the absence or presence of compounds were analysed by quantitative PCR. Next to the detection of integrated DNA (proviral DNA), the production of 2LTR-circles formed by circularisation of unintegrated DNA was monitored. Specific inhibition of the integration of viral DNA into the genome was typically associated with accumulation of 2LTR-circles in the nucleus.

MT4 cells were infected with HIV at high MOI by centrifugation for 60 min at 1200 g. After infection cells were incubated in the presence of compound in 24-well plates (10^6 c/well) for 16h, and DNA was extracted using the QiaAmp DNA mini kit (Qiagen). After normalization, 2LTR-circles and integrated DNA were quantified by real-time PCR using the appropriate primers and probe (cfr. reference Butler et al.). Reactions were analysed using the ABI Prism 5700 sequence detection system (Applied Biosystems).

DNA was analyzed for integration (Alu-PCR) and 2LTR-circles, 16h after infection. DNA was also analyzed for viral cDNA synthesis, 4h after infection. Results are shown in Table 2.

Table 2

	Integration		
Compound	**Alu-PCR**	**2LTR-circles**	**Conclusion**
Control	+	+	
Reference compound	-	+++	Integrase
NNRTI	-	-	RT
Compound 1	-	+++	Integrase
Compound 2	-	+++	Integrase



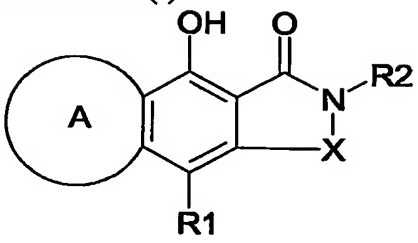
Reference compound with known integrase inhibitory activity

In Table 2, symbol "+" indicates the amount of DNA copies in the absence of a compound, that is in the control reaction, for both integrated DNA and 2LTR-circles:

- "++" symbol indicates a 2-to-5 fold increase in the amount of DNA copies in comparison with the control level
- "+++" symbol indicates an increase in the amount of DNA copies > 5 in comparison with the control level
- "-" symbol indicates an amount of DNA copies near or below the detection limit.

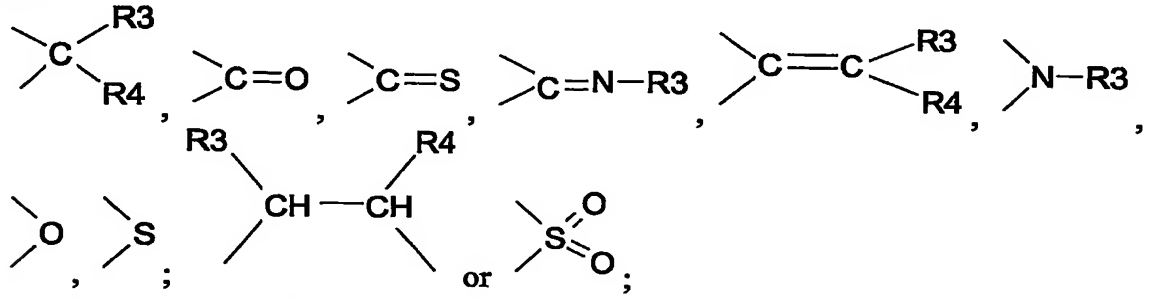
CLAIMS

1. A compound having the formula (I)



its N-oxide, salt, stereoisomeric form, racemic mixture, prodrug, ester or metabolite thereof, wherein

X is



A, also mentioned as "A-ring", together with the two carbons of the phenyl ring to which it is attached forms a monocyclic aryl or a monocyclic Het^2;

R^1 is hydrogen, halogen, nitro, cyano, sultam, sultim, C_{3-7}cycloalkyl, $C(=O)$-R^5, $S(=O)_y$-R^6, OR^7, NR^8R^9, $C(=NR^8)$-R^5, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^5, $S(=O)_y$-R^6, OR^7, and NR^8R^9;

R^2 is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^5, $S(=O)_y$-R^6, OR^7, NR^8R^9, $C(=NR^8)$-R^5, or optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^5, $S(=O)_y$-R^6, OR^7, and NR^8R^9;

R^3 is hydrogen, halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, $C(=O)$-R^5, $S(=O)_y$-R^6, OR^7, NR^8R^9, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, $C(=O)$-R^5, OR^7, and NR^8R^9;

R^4 is hydrogen, halogen, nitro, cyano, C_{3-7}cycloalkyl or C_{1-6}alkyl;
y represents an integer being zero, one or two;
R^5 is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, C(=O)-R^{10}, OR^{12}, NR^8R^{13}, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, C(=O)-R^{10}, $S(=O)_y$-R^{11}, OR^{12}, and NR^8R^{13};
R^6 is hydrogen, aryl, C_{3-7}cycloalkyl, Het^1, Het^2, OR^{12}, NR^8R^{13}, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, C(=O)-R^{10}, $S(=O)_y$-R^{11}, OR^{12}, and NR^8R^{13};
R^7 is hydrogen, aryl, C_{3-7}cycloalkyl, Het^1, Het^2, C(=O)-R^{10}, $S(=O)_y$-R^{11}, or optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano,C_{3-7}cycloalkyl, aryl, Het^1, Het^2, C(=O)-R^{10}, $S(=O)_y$-R^{11}, OR^{12}, and NR^8R^{13};
R^8 is hydrogen, aryl, Het^1, Het^2, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl or polyhaloC_{1-6}alkyl;
R^9 is hydrogen, aryl, C_{3-7}cycloalkyl, Het^1, Het^2, C(=O)-R^{10}, $S(=O)_y$-R^{11}, C(=NR^8)-R^5, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano,C_{3-7}cycloalkyl, aryl, Het^1, Het^2, C(=O)-R^{10}, $S(=O)_y$-R^{11}, OR^{12} and NR^8R^{13};
R^{10} is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, C(=O)-R^8, C(=O)-OR^8, C(=O)-NR^8R^8, OR^8, O-C(=O)-R^8, O-$S(=O)_y$-R^8, $S(=O)_y$-R^8, NR^8R^8, NR^8-C(=O)-R^8, NR^8-$S(=O)_y$-R^8, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, C(=O)-R^8, C(=O)-OR^8, C(=O)-NR^8R^8, $S(=O)_y$-R^8, $S(=O)_y$-OR^8, $S(=O)_y$-NR^8R^8, OR^8, O-C(=O)-R^8, O-$S(=O)_y$-R^8, NR^8R^8, NR^8-C(=O)-R^8, and NR^8-$S(=O)_y$-R^8;
R^{11} is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, OR^8, O-C(=O)-R^8, O-$S(=O)_y$-R^8, NR^8R^8, NR^8-C(=O)-R^8, NR^8-$S(=O)_y$-R^8, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each

independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)-R^8$, $C(=O)-OR^8$, $C(=O)-NR^8R^8$, $S(=O)_y-R^8$, $S(=O)_y-OR^8$, $S(=O)_y-NR^8R^8$, OR^8, $O-C(=O)-R^8$, $O-S(=O)_y-R^8$, NR^8R^8, $NR^8-C(=O)-R^8$, and $NR^8-S(=O)_y-R^8$;

R^{12} is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)-R^8$, $C(=O)-OR^8$, $C(=O)-NR^8R^8$, $S(=O)_y-R^8$, $S(=O)_y-OR^8$, $S(=O)_y-NR^8R^8$, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)-R^8$, $C(=O)-OR^8$, $C(=O)-NR^8R^8$, $S(=O)_y-R^8$, $S(=O)_y-OR^8$, $S(=O)_y-NR^8R^8$, OR^8, $O-C(=O)-R^8$, $O-S(=O)_y-R^8$, NR^8R^8, $NR^8-C(=O)-R^8$, and $NR^8-S(=O)_y-R^8$;

R^{13} is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)-R^8$, $C(=O)-OR^8$, $C(=O)-NR^8R^8$, $S(=O)_y-R^8$, $S(=O)_y-OR^8$, $S(=O)_y-NR^8R^8$, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)-R^8$, $C(=O)-OR^8$, $C(=O)-NR^8R^8$, $S(=O)_y-R^8$, $S(=O)_y-OR^8$, $S(=O)_y-NR^8R^8$, OR^8, $O-C(=O)-R^8$, $O-S(=O)_y-R^8$, NR^8R^8, $NR^8-C(=O)-R^8$, and $NR^8-S(=O)_y-R^8$;

R^{14} is hydrogen, phenyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl;

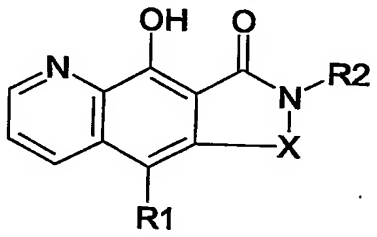
aryl as a group or part of a group represents a monocyclic or polycyclic aromatic or a partially saturated monocyclic or polycyclic carbocycles wherein any such carbocycle within the meaning of aryl may have up to 14 carbon atoms and may be optionally substituted with one or more substituents independently selected from halogen, nitro, oxo, cyano, C_{3-7}cycloalkyl, Het^1, Het^2, $C(=O)-R^8$, $S(=O)_y-R^{14}$, OR^{14}, $NR^{14}R^{14}$, $NR^{14}-O-C(=O)-R^{14}$, $NR^{14}-C_{1-6}$alkanediyl-$NR^{14}-Het^1$, $NR^{14}-C_{1-6}$alkanediyl-$NR^{14}-Het^2$, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl, optionally polysubstituted C_{2-6}alkynyl and optionally polysubstituted phenyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, phenyl, $C(=O)-R^{14}$, OR^{14}, Het^1, Het^2, $C(=O)-Het^1$, $C(=O)-Het^2$, and $NR^{14}R^{14}$; and whereby the optional substituents on phenyl are each independently selected from halogen, hydroxy, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, $O-C_{1-6}$alkyl, and C_{1-6}alkanediyl-$NR^{14}R^{14}$;

Het^1 as a group or part of a group represents a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle having 3 to 14 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen and sulfur, and which may be optionally substituted on a carbon atom or where possible a nitrogen atom with one or more substituents independently selected from halogen, nitro, oxo, cyano, C_{3-7}cycloalkyl, $C(=O)-R^{14}$, $S(=O)_y-R^{14}$, OR^{14}, $NR^{14}R^{14}$,

NR^{14}-O-C(=O)-R^{14}, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl, optionally polysubstituted C_{2-6}alkynyl and optionally polysubstituted phenyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, phenyl, C(=O)-R^{14}, OR^{14}, and $NR^{14}R^{14}$; and whereby the optional substituents on phenyl are each independently selected from halogen, hydroxy, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, O-C_{1-6}alkyl, and C_{1-6}alkanediyl-$NR^{14}R^{14}$;

Het^2 as a group or part of a group represents an aromatic monocyclic, bicyclic or tricyclic heterocycle having 5 to 14 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen and sulfur, and which may be optionally substituted on a carbon atom or where possible a nitrogen atom with one or more substituents independently selected from halogen, nitro, oxo, cyano, C_{3-7}cycloalkyl, C(=O)-R^{14}, $S(=O)_y$-R^{14}, OR^{14}, $NR^{14}R^{14}$, NR^{14}-O-C(=O)-R^{14}, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl, optionally polysubstituted C_{2-6}alkynyl and optionally polysubstituted phenyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, phenyl, C(=O)-R^{14}, OR^{14}, and $NR^{14}R^{14}$; and whereby the optional substituents on phenyl are each independently selected from halogen, hydroxy, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, O-C_{1-6}alkyl, and C_{1-6}alkanediyl-$NR^{14}R^{14}$.

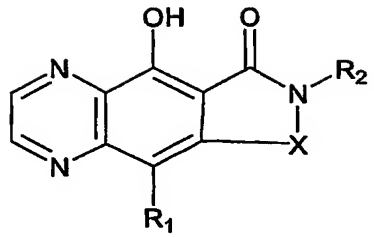
2. A compound as claimed in claim 1 wherein the compound has the formula (IIa)



whereby

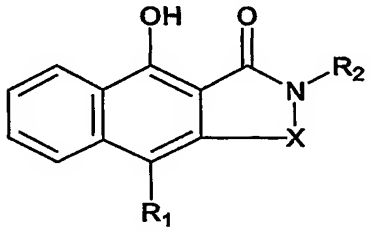
the pyridinyl ring may optionally be substituted with halogen or optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl, optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, phenyl, C(=O)-R^{14}, OR^{14}, Het^1, Het^2, C(=O)-Het^1, C(=O)-Het^2, and $NR^{14}R^{14}$.

3. A compound as claimed in claim 1 wherein the compound has the formula (IIb)



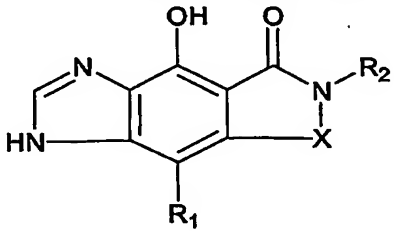
whereby the pyrazinyl ring may optionally be substituted with halogen or optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl, optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, phenyl, C(=O)-R^{14}, OR^{14}, Het^1, Het^2, C(=O)-Het^1, C(=O)-Het^2, and $NR^{14}R^{14}$.

4. A compound as claimed in claim 1 wherein the compound has the formula (IIc)



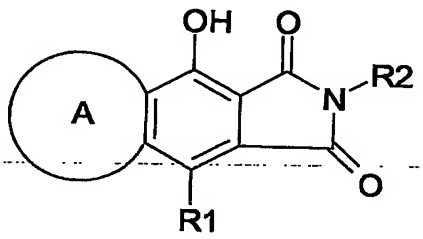
whereby the phenyl ring may optionally be substituted with halogen or optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl, optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, phenyl, C(=O)-R^{14}, OR^{14}, Het^1, Het^2, C(=O)-Het^1, C(=O)-Het^2, and $NR^{14}R^{14}$.

5. A compound as claimed in claim 1 wherein the compound has the formula (IId)



whereby the imidazolyl ring may optionally be substituted with halogen or optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl, optionally polysubstituted C_{2-6}alkynyl; whereby the optional substituents on C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are each independently selected from halogen, nitro, cyano, phenyl, C(=O)-R^{14}, OR^{14}, Het^1, Het^2, C(=O)-Het^1, C(=O)-Het^2, and $NR^{14}R^{14}$.

6. A compound as claimed in claim 1 wherein the compound has the formula (III)



7. A compound as claimed in any one of claims 1 to 6 wherein

X is -C(=O)-;

R^1 is $-OR^7$;

R^2 is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, or optionally substituted C_{1-6}alkyl; whereby the optional substituent on C_{1-6}alkyl is selected from C_{3-7}cycloalkyl, aryl, Het^1, Het^2, and preferably is C_{3-7}cycloalkyl, aryl, Het^1.

8. A pharmaceutical composition, comprising an effective amount of at least one compound as claimed in any one of claims 1 to 7, and a pharmaceutically acceptable excipient.

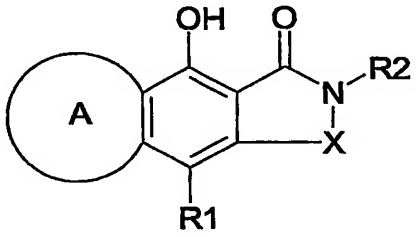
9. A compound as claimed in any one of claims 1 to 7 for use as a medicine.

10. The use of a compound as claimed in any one of claims 1 to 7 in the manufacture of a medicament for treating or combating infection or disease associated with retrovirus infection in a mammal.

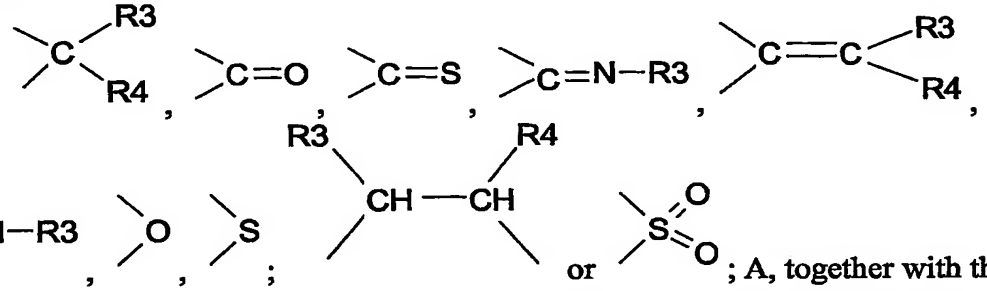
ABSTRACT

HIV INTEGRASE INHIBITORS

The present invention concerns the compounds having the formula (I),



N-oxides, salts, stereoisomeric forms, racemic mixtures, prodrugs, esters and metabolites thereof wherein

X is 

; A, together with the two carbons of the phenyl ring to which it is attached forms a monocyclic aryl or a monocyclic Het^2; R^1 is hydrogen, halo, nitro, cyano, sultam, sultim, C_{3-7}cycloalkyl, $C(=O)$-R^5, $S(=O)_y$-R^6, OR^7, NR^8R^9, $C(=NR^8)$-R^5, optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl; R^2 is hydrogen, C_{3-7}cycloalkyl, aryl, Het^1, Het^2, $C(=O)$-R^5, $S(=O)_y$-R^6, OR^7, NR^8R^9, $C(=NR^8)$-R^5, or optionally polysubstituted C_{1-6}alkyl, optionally polysubstituted C_{2-6}alkenyl or optionally polysubstituted C_{2-6}alkynyl.

It further relates to their use as HIV integrase inhibitors, processes for their preparation as well as pharmaceutical compositions and diagnostic kits comprising them. It also concerns combinations thereof with other anti-retroviral agents, and to their use in assays as reference compounds or as reagents.

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